Drug Class Review

Proton Pump Inhibitors

Final Report Update 5

May 2009

Update 4: May 2006
Update 3: May 2005
Update 2: April 2004
Update 1: April 2003
Original Report: November 2002

The literature on this topic is scanned periodically.

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use, or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

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EVIDENCE TABLES
Published in a separate document

The medical literature relating to this topic is scanned periodically. (See http://www.ohsu.edu/ohsuedu/research/policycenter/DERP/about/methods.cfm for description of scanning process). Prior versions of this report can be accessed at the DERP website.

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INTRODUCTION

Proton pump inhibitors decrease secretion of gastric acid. They act by blocking the last enzyme in the system that actively transports acid from gastric parietal cells into the gastrointestinal lumen, hydrogen–potassium adenosine triphosphatase, also known as the proton pump. Omeprazole, the first drug in this class, was introduced in 1989. Since then, 4 other proton pump inhibitors have been introduced: lansoprazole (1995), rabeprazole (1999), pantoprazole (2000), and esomeprazole (2001). In 2003 omeprazole became available over-the-counter in the United States. The formulation for the over-the-counter product is omeprazole magnesium, available in other countries as omeprazole multiple unit pellet system. Omeprazole is also available in combination with sodium bicarbonate (Zegerid). Table 1 provides an accounting of indications of different proton pump inhibitors.

Proton pump inhibitors are mainly used to treat symptoms of gastroesophageal reflux disease and gastritis. Often, they are used only after therapy with histamine-2 (H2) receptor antagonists, commonly called H2 blockers, has been unsuccessful for symptoms of reflux. Proton pump inhibitors also are used to treat peptic ulcers (duodenal and gastric) and drug-induced ulcers, such as those associated with nonsteroidal anti-inflammatory drugs; the bacterium that causes ulcers, *Helicobacter pylori,* is eradicated by treatment with a proton pump inhibitor and antibiotics. Proton pump inhibitors also are used to promote healing of erosive esophagitis. Esophagitis can lead to scarring and narrowing of the esophagus (stricture) or to Barrett esophagus, which is a risk factor for esophageal cancer.

Evidence-based reviews usually emphasize health outcomes—events or conditions that patients can feel or experience. Heartburn, waking at night, acid regurgitation, and quality of life are health outcomes. But severity of symptoms is not a reliable indicator of esophagitis; patients without esophagitis can experience severe heartburn, and some patients who have esophagitis have no symptoms. Consequently, esophagitis is diagnosed by direct visualization via endoscopy. Esophagitis appears as a tear, break, or ulceration in the lining of the esophagus. When esophagitis has healed, the ulceration has been completely reepithelialized, as viewed during endoscopy. This endoscopically verified healing often is used as an intermediate outcome measure for esophagitis.

For ulcer disease, quick relief of symptoms is an important health outcome. But in the long run, the most important determinant of functional status and quality of life is prevention of recurrence of ulcers and their complications (bleeding, hospitalization, and death). Historically, studies of proton pump inhibitors for ulcer disease have been too short to address these outcomes directly. So instead, they report intermediate outcome measures. In the past the most common intermediate outcome measure was endoscopic healing, meaning that on endoscopy after treatment the ulcer is gone. But because ulcer disease tends to recur even when the initial ulcer has completely healed, endoscopic healing, while important as a predictor of relapse, is an imperfect indicator of long-term morbidity from ulcer disease. Since the discovery that *Helicobacter pylori* causes many peptic ulcers, eradication of *Helicobacter pylori* has emerged as a more important indicator of the long-term outcome of treatment. Long-term studies have shown that eradication reduces the risk of ulcers and ulcer complications for several years.

Table 1. Proton pump inhibitors and their US Food and Drug Administration-approved indications

Active ingredient	Trade name	Dosage form	Duodenal or gastric ulcer	GERD	Erosive esophagitis maintenance	Erosive esophagitis treatment	NSAID-induced ulcer
Omeprazole	Prilosec®	Oral capsule	X	XX	X	XX	X
		Oral suspension	X	XX	X	XX	X
	Losec® (Canada)	Oral capsule	X	X	-	-	X
	Prilosec OTC®[a]	Oral tablet	-	X[a]	-	-	-
Omeprazole/ sodium bicarbonate	Zegerid®[a]	Oral suspension	-	X	X	X	-
		Oral capsule	X	X	X	X	-
		Oral chewable tablet	X	X	X	X	-
Lansoprazole	Prevacid®	Oral capsule	X	XX	X	XX	X
		Oral suspension	X	XX	X	XX	X
		Oral tablet	X	X	X	XX	X
	Prevacid FasTab® (Canada)	Oral tablet	X	XX	-	XX	X
Pantoprazole	Protonix®	Oral tablet	-	-	X	X	-
		Oral suspension	-	-	X	X	-
	Pantoloc® (Canada)	Oral tablet	X	X	-	-	X
Rabeprazole	Aciphex®	Oral tablet	X[b]	XX[c]	X	X	-
	Pariet® (Canada)	Oral tablet	X	X	-	-	-
Esomeprazole	Nexium®	Oral capsule	-	XX	X	X	X
		Oral suspension	-	XX	X	X	X

Abbreviations: GERD, gastroesophageal reflux disease; NSAID, nonsteroidal anti-inflammatory drug.
X: Adults; XX: Pediatrics and adults.
[a] Not available in Canada. Indication = treatment of frequent heartburn (>2 times weekly). Heartburn is listed as the only "use" for Prilosec OTC per product labeling description.
[b] Duodenal ulcers only.
[c] For patients 12 years and over.

Purpose and Limitations of Systematic Reviews

Systematic reviews, also called evidence reviews, are the foundation of evidence-based practice. They focus on the strength and limits of evidence from studies about the effectiveness of a clinical intervention. Systematic reviews begin with careful formulation of research questions. The goal is to select questions that are important to patients and clinicians then to examine how well the scientific literature answers those questions. Terms commonly used in systematic reviews, such as statistical terms, are provided in Appendix A and are defined as they apply to reports produced by the Drug Effectiveness Review Project.

Systematic reviews emphasize the patient's perspective in the choice of outcome measures used to answer research questions. Studies that measure health outcomes (events or conditions that the patient can feel, such as fractures, functional status, and quality of life) are preferred over studies of intermediate outcomes (such as change in bone density). Reviews also emphasize measures that are easily interpreted in a clinical context. Specifically, measures of *absolute risk* or the probability of disease are preferred to measures such as relative risk. The difference in absolute risk between interventions depends on the number of events in each group, such that the difference (absolute risk reduction) is smaller when there are fewer events. In contrast, the difference in relative risk is fairly constant between groups with different baseline risk for the event, such that the difference (relative risk reduction) is similar across these groups. Relative risk reduction is often more impressive than absolute risk reduction. Another useful measure is the *number needed to treat* (or harm). The number needed to treat is the number of patients who would need be treated with an intervention for 1 additional patient to benefit (experience a positive outcome or avoid a negative outcome). The absolute risk reduction is used to calculate the number needed to treat.

Systematic reviews weigh the quality of the evidence, allowing a greater contribution from studies that meet high methodological standards and, thereby, reducing the likelihood of biased results. In general, for questions about the relative benefit of a drug, the results of well-executed randomized controlled trials are considered better evidence than results of cohort, case-control, and cross-sectional studies. In turn, these studies provide better evidence than uncontrolled trials and case series. For questions about tolerability and harms, observational study designs may provide important information that is not available from controlled trials. Within the hierarchy of observational studies, well-conducted cohort designs are preferred for assessing a common outcome. Case-control studies are preferred only when the outcome measure is rare and the study is well conducted.

Systematic reviews pay particular attention to whether results of *efficacy studies* can be generalized to broader applications. Efficacy studies provide the best information about how a drug performs in a controlled setting. These studies attempt to tightly control potential confounding factors and bias; however, for this reason the results of efficacy studies may not be applicable to many, and sometimes to most, patients seen in everyday practice. Most efficacy studies use strict eligibility criteria that may exclude patients based on their age, sex, adherence to treatment, or severity of illness. For many drug classes, including the antipsychotics, unstable or severely impaired patients are often excluded from trials. In addition, efficacy studies frequently exclude patients who have comorbid disease, meaning disease other than the one under study. Efficacy studies may also use dosing regimens and follow-up protocols that are impractical in typical practice settings. These studies often restrict options that are of value in actual practice, such as combination therapies and switching to other drugs. Efficacy studies also

often examine the short-term effects of drugs that in practice are used for much longer periods. Finally, efficacy studies tend to assess effects by using objective measures that do not capture all of the benefits and harms of a drug or do not reflect the outcomes that are most important to patients and their families.

Systematic reviews highlight studies that reflect actual clinical *effectiveness* in unselected patients and community practice settings. Effectiveness studies conducted in primary care or office-based settings use less stringent eligibility criteria, more often assess health outcomes, and have longer follow-up periods than most efficacy studies. The results of effectiveness studies are more applicable to the "average" patient than results from the highly selected populations in efficacy studies. Examples of effectiveness outcomes include quality of life, frequency or duration of hospitalizations, social function, and the ability to work. These outcomes are more important to patients, family, and care providers than surrogate or intermediate measures, such as scores based on psychometric scales.

Efficacy and effectiveness studies overlap. For example, a study might use very narrow inclusion criteria like an efficacy study, but, like an effectiveness study, might examine flexible dosing regimens, have a long follow-up period, and measure quality of life and functional outcomes. For this report we sought evidence about outcomes that are important to patients and would normally be considered appropriate for an effectiveness study. However, many of the studies that reported these outcomes were short-term and used strict inclusion criteria to select eligible patients. For these reasons, it was neither possible nor desirable to exclude evidence based on these characteristics. Labeling a study as either an efficacy or an effectiveness study, although convenient, is of limited value; it is more useful to consider whether the patient population, interventions, time frame, and outcomes are relevant to one's practice or to a particular patient.

Studies anywhere on the continuum from efficacy to effectiveness can be useful in comparing the clinical value of different drugs. Effectiveness studies are more applicable to practice, but efficacy studies are a useful scientific standard for determining whether characteristics of different drugs are related to their effects on disease. Systematic reviews thoroughly cover the efficacy data in order to ensure that decision makers can assess the scope, quality, and relevance of the available data. This thoroughness is not intended to obscure the fact that efficacy data, no matter how large the quantity, may have limited applicability to practice. Clinicians can judge the relevance of studies' results to their practice and should note where there are gaps in the available scientific information.

Unfortunately, for many drugs there exist few or no effectiveness studies and many efficacy studies. Yet clinicians must decide on treatment for patients who would not have been included in controlled trials and for whom the effectiveness and tolerability of the different drugs are uncertain. Systematic reviews indicate whether or not there exists evidence that drugs differ in their effects in various subgroups of patients, but they do not attempt to set a standard for how results of controlled trials should be applied to patients who would not have been eligible for them. With or without an evidence report, these decisions must be informed by clinical judgment.

In the context of development of recommendations for clinical practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of an intervention are based on strong evidence from clinical studies. By themselves, they do not say what to do. Judgment, reasoning, and applying one's values under conditions of uncertainty must also play a role in decision making. Users of an

evidence report must also keep in mind that *not proven* does not mean *proven not*; that is, if the evidence supporting an assertion is insufficient, it does not mean the assertion is untrue. The quality of the evidence on effectiveness is a key component, but not the only component, in making decisions about clinical policy. Additional criteria include acceptability to physicians and patients, potential for unrecognized harm, applicability of the evidence to practice, and consideration of equity and justice.

Scope and Key Questions

The purpose of this review is to compare the benefits and harms of different proton pump inhibitors. The Oregon Evidence-based Practice Center wrote preliminary key questions, identifying the populations, interventions, and outcomes of interest, and, based on these, the eligibility criteria for studies. These were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project. The participating organizations of the Drug Effectiveness Review Project are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The participating organizations approved the following key questions to guide Update 5 of this review:

1. What is the comparative effectiveness of different proton pump inhibitors in patients with symptoms of gastroesophageal reflux disease?

2. What is the comparative effectiveness of different proton pump inhibitors in treating peptic ulcer and nonsteroidal anti-inflammatory drug-induced ulcer?

3. What is the comparative effectiveness of different proton pump inhibitors in preventing ulcer in patients taking a nonsteroidal anti-inflammatory drug?

4. What is the comparative effectiveness of different proton pump inhibitors in eradicating *Helicobacter pylori* infection?

5. Is there evidence that a particular treatment strategy is more effective or safer than another (for example, stepping down to a lower dose, treatment as needed compared with daily treatment, high dose compared with standard dose, or switching to an H2 antagonist) for treatment longer than 8 weeks in patients with gastroesophageal reflux disease or ulcer?

6. What are the comparative safety and adverse events of different proton pump inhibitors in patients being treated for symptoms of gastroesophageal reflux disease, peptic ulcer, and nonsteroidal anti-inflammatory drug-induced ulcer?

7. Are there subgroups of patients based on demographics, other medications, or comorbidities (including nasogastric tubes and inability to swallow solid oral medication) for which a particular proton pump inhibitor or preparation is more effective or associated with fewer adverse effects?

METHODS

Literature Search

To identify articles relevant to each key question, we searched the Cochrane Library (4th Quarter 2008), Medline (1966- week 2 of November 2008), Embase (1980-3rd Quarter 2004), and reference lists of review articles. In electronic searches, we combined terms for gastroesophageal reflux and peptic ulcer with terms for proton pump inhibitors and particular research designs. (See Appendix B for complete search strategy.) Pharmaceutical manufacturers were invited to submit dossiers, including citations. All citations were imported into an electronic database (EndNote X1).

Update 5 added a key question (Key Question 5) addressing different treatment strategies. To identify citations relevant to the new question but published before the literature search for this update, we searched the EndNote library of citations from all previous versions of this report, looking for citations that met criteria for this new question.

Study Selection

The abstracts of all citations identified in literature searches and dossiers were assessed for inclusion using the predetermined criteria specified in the key questions. For abstracts that met these criteria, full-text articles were retrieved and inclusion criteria reapplied. Citation and full-text review were conducted by one reviewer and checked by a second. Disagreements were resolved by consensus.

We included English-language reports of randomized controlled trials of at least 4 weeks' duration in adult outpatients with symptoms of gastroesophageal reflux, peptic ulcer, or nonsteroidal anti-inflammatory drug-induced ulcer. Included interventions were a proton pump inhibitor (omeprazole, lansoprazole, pantoprazole, rabeprazole, or esomeprazole) compared with proton pump inhibitor, other ulcer drug (H2 receptor antagonist, prokinetic agent, or antacid), placebo, surgery, or antibiotics. For adverse effects, we also included observational studies. Outcomes measured were symptoms, functional outcomes, endoscopic healing, eradication of *Helicobacter pylori*, quality of life, and adverse effects. We excluded reports that were published as only abstracts (see Appendix C).

To evaluate *efficacy* we included only randomized controlled trials. The validity of controlled trials depends on how they are designed. Randomized, properly blinded clinical trials are considered the highest level of evidence for assessing efficacy.[1-3] Clinical trials that are not randomized or blinded, and those that have other methodological flaws, are less reliable but are also discussed in our report.

Trials that compared one proton pump inhibitor with another provided direct evidence of comparative efficacy and adverse event rates. We did not examine in detail placebo-controlled or active-control trials when head-to-head trials were available. In theory, trials that compare proton pump inhibitors with H2 receptor antagonists or placebos also can provide evidence about efficacy. However, the efficacy of proton pump inhibitors in different trials can be difficult to interpret because of differences between patients.

To supplement our analyses of published results, we requested and received from the trial funders additional data for 2 published trials[4, 5] and 1 trial[6] that was submitted to the US Food and Drug Administration but not published.

To evaluate *adverse events*, we included clinical trials and observational cohort studies. Clinical trials are often not designed to assess adverse events and may select only low-risk patients (in order to minimize drop-out rate) or use inadequately rigorous methodology for assessing adverse events. Observational studies designed to assess adverse event rates may include broader populations, carry out observations over a longer period, use higher quality methodological techniques for assessing adverse events, or examine larger sample sizes.

Data Abstraction

The following data were abstracted from included studies: study design; setting; population characteristics (including sex, age, ethnicity, diagnosis); eligibility and exclusion criteria; interventions (dose and duration); comparisons; numbers screened, eligible, enrolled, and lost to follow-up; method of outcome ascertainment; and results for each outcome. We recorded intention-to-treat results if they were available and the trial did not report high overall loss to follow-up. Data were abstracted by one reviewer and checked for accuracy by a second; disagreements were resolved by consensus.

Validity Assessment

We assessed the internal validity (quality) of trials based on the predefined criteria listed in Appendix D. These criteria are based on criteria developed by the US Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination (United Kingdom) for assessing study quality.[2, 7] We rated the internal validity of each trial on the basis of the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; maintenance of comparable groups; adequate reporting of dropouts, attrition, crossover, adherence, and contamination; loss to follow-up; and the use of intention-to-treat analysis. Trials that had a fatal flaw in 1 or more categories were rated poor quality. Trials that met all criteria were rated good quality. The remainder were rated fair quality. As the fair-quality category is broad, studies with this rating vary in their strengths and weaknesses: The results of some fair-quality studies are *likely* to be valid, while others are only *probably* valid. A poor-quality trial is not valid; the results are at least as likely to reflect flaws in the study design as a true difference between the compared drugs. External validity of trials was assessed based on whether the publication adequately described the study population, whether patients in the study were similar to patients in the target population in whom the intervention will be applied, and whether the treatment received by the control group was reasonably representative of standard practice. We also recorded the funding source and role of the funder.

Appendix D also shows the criteria we used to rate observational studies of adverse events. These criteria reflect aspects of the study design that are particularly important for assessing adverse event rates. We rated observational studies as good quality for adverse event assessment if they adequately met 6 or more of the 7 predefined criteria, fair if they met 3 to 5 criteria, and poor if they met 2 or fewer criteria.

Overall quality rating for an individual study was based on ratings of internal and external validity of the trial. A particular randomized trial might receive 2 quality ratings, 1 for efficacy and another for adverse events. The overall strength of evidence for a particular key question reflects the quality, consistency, and power of the set of studies relevant to the question.

Data Synthesis

We constructed evidence tables showing the study characteristics, quality ratings, and results for all included studies. We reviewed studies using a hierarchy-of-evidence approach, in which the best evidence was the focus of our synthesis for each question, population, intervention, and outcome addressed. Meta-analyses were conducted where possible. *Differences* in healing rates (ulcers and esophagitis) between drugs based on head-to-head trials are expressed as the percent risk difference, defined as the difference between the proportions healed in 2 groups of patients at a specified time-point. For example, if at 4 weeks 80% of patients in group A have only healed lesions and 75% in group B have only healed lesions, then the risk difference between the groups is 5%. A measure of the variance around these estimates, the 95% confidence interval (CI) is also reported. If the 95% CI includes 0, then the difference is not statistically significant. Meta-analysis was done using RevMan software using a random-effects model. (RevMan, Version 5.0, The Cochrane Collaboration, 2008).

To determine healing and symptom resolution *rates* for *individual* drugs, we performed a meta-analysis by using a random-effects model controlling for the effect of the study. For example, the healing rate for Drug A might be calculated as 81% based on 7 head-to-head trials, and Drug B might have a rate of 83% based on 4 head-to-head trials.. This analysis was conducted using SAS 9.1 (SAS Institute Inc., Cary, NC, USA using data on each individual drug from head-to-head trials.

Similarly, we conducted random-effects logistic meta-regression to estimate rates of healing associated with *individual* drugs based on studies comparing a proton pump inhibitor with a H2 receptor antagonist. The rate of healing with the proton pump inhibitor was adjusted for healing rate with H2 receptor antagonist within the same study. The model stratified by type of proton pump inhibitor (lansoprazole, omeprazole, pantoprazole, and rabeprazole). Posterior distributions were simulated using WinBUGS software version 1.4.3 (Medical Research Council and Imperial College School of Medicine at St Mary's, London).[8]

Peer and Public Review

The Original report underwent a review process that involved solicited peer review from clinical experts. Their comments were reviewed and, where possible, incorporated into the final document. The comments received and the author's proposed actions were reviewed by the representatives of the participating organizations of the Drug Effectiveness Review Project prior to finalization of the report. Names of peer reviewers for Drug Effectiveness Review Project reports are listed at www.ohsu.edu/drugeffectiveness. Peer reviewers have a maximum of 3 weeks for review and comment. They are asked to submit their comments in a standardized form in order to maintain consistent handling of comments across reports and to allow the Drug Effectiveness Review Project team to address all comments adequately.

The Drug Effectiveness Review Project process allows for a 2-week public comment period prior to finalization of the current report. Draft reports are posted on the Drug Effectiveness Review Project web site and interested individuals or organizations have the ability to review the complete draft report and submit comments. For Update 5 of this report, we received comments from 2 pharmaceutical companies.

RESULTS

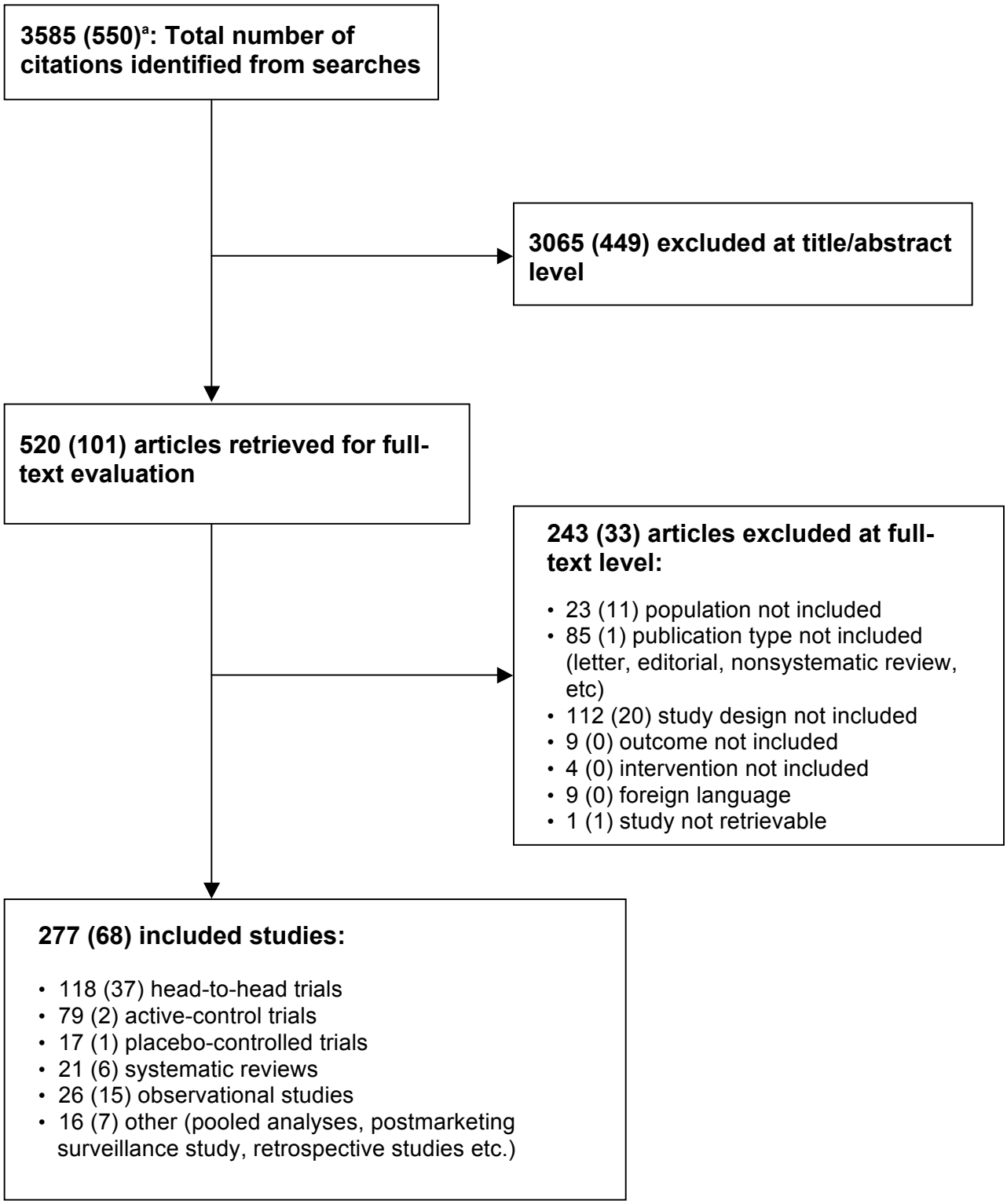
Overview

Our literature searches identified 550 new citations for Update 5: 376 from Medline, 57 from Cochrane Central Register of Controlled Trials, 45 from dossiers submitted by the manufacturers of esomeprazole and rabeprazole, 31 from Cochrane Database of Systematic Reviews, 29 from Database of Abstracts of Reviews of Effects, 7 from public comment on the draft of this report, and 5 from reference lists of included review articles. Of these 68 were ultimately included (see Figure 1).

We excluded trials when the study was reported only as an abstract, contained no original data, contained no included outcome measure, did not have an included study design, did not use an included drug or used combined drug therapy where the effect of the proton pump inhibitor could not be distinguished, did not evaluate an included patient population, or was reported in a language other than English. Figure 1 summarizes the flow of study inclusion and exclusion. No study of omeprazole in combination with sodium bicarbonate (Zegerid) met inclusion criteria.

There is controversy about the appropriateness of dose comparisons in head-to-head trials comparing esomeprazole with omeprazole. The US Food and Drug Administration's clinical review of esomeprazole indicates that esomeprazole 40 mg is "pharmacodynamically thrice that of the s-isomer" in omeprazole 20 mg (see US Food and Drug Administration Medical Review, executive summary, page 4).[9] While the doses approved by the US Food and Drug Administration for treatment of erosive esophagitis are 20 to 40 mg daily for esomeprazole, and 20 mg daily for omeprazole (both for 4 to 8 weeks), because of differences in drug chemistry and pharmacology, there is no clear equivalent dose of omeprazole and esomeprazole.

Figure 1. Results of literature search



[a] Numbers in parentheses are results of the literature search new to Update 5.

Key Question 1. What is the comparative efficacy of different proton pump inhibitors in patients with symptoms of gastroesophageal reflux disease?

Summary

Symptom relief and healing in patients with erosive esophagitis

- Among 16 head-to-head trials, those with comparable doses did not find differences in symptom relief or healing of esophagitis.
- The only difference between proton pump inhibitors on the outcome of complete symptom relief at 4 weeks was in the comparison of esomeprazole 40 mg with omeprazole 20 mg; the pooled risk difference in 3 trials was 8% (95% CI 3 to 13), with a number needed to treat of 13.
- Time to relief of heartburn was similar for all proton pump inhibitors in head-to-head trials, but the methods used to measure and report this outcome varied in the 14 studies.
- Good evidence showed no difference between omeprazole, lansoprazole, pantoprazole, and rabeprazole for healing of esophagitis. Thirteen head-to-head trials found these 4 proton pump inhibitors to be equally effective in healing at 4 and 8 weeks.
- Pooled analysis of 4- and 8-week healing rates from 4 trials of esomeprazole 40 mg compared to omeprazole 20 mg indicated esomeprazole to be superior; risk difference 7% (95% CI 1 to 12) and a number needed to treat of 14 and 5% (95% CI 1 to 9), number needed to treat = 20, respectively.
- Three trials compared esomeprazole 40 mg with lansoprazole 30 mg. The pooled difference in healing rate was significantly greater with esomeprazole at 4 and 8 weeks, risk differences 5% (95% CI 2 to 7) and 3% (95% CI 1 to 5), respectively.
- Evidence on the comparison of esomeprazole 40 mg and pantoprazole 40 mg was mixed, with 2 studies finding esomeprazole superior and 2 finding no difference in healing rates. Pooled analysis of 3 trials with similar populations finds that esomeprazole was superior to pantoprazole at 4 weeks (risk difference 5%, 95% CI 2 to 8), but not at 8 weeks (risk difference 1%, 95% CI –3 to 5).

Healing in moderate to severe erosive esophagitis

- Esomeprazole 40 mg was more effective at healing esophagitis at 4 and 8 weeks than omeprazole 20 mg and lansoprazole 30 mg.
- The pooled risk difference in 3 studies comparing omeprazole 20 mg with esomeprazole 40 mg was 16% at 4 weeks and 13% at 8 weeks (number needed to treat = 6 at 4 weeks, 8 at 8 weeks).
- The pooled risk difference in 2 studies comparing lansoprazole 30 mg with esomeprazole 40 mg was 8% at 4 weeks and 9% at 8 weeks (number needed to treat = 13 at 4 weeks, 11 at 8 weeks).
- Evidence was mixed on differences between esomeprazole 40 mg and pantoprazole 40 mg.
    - At 4 weeks, esomeprazole 40 mg had a higher healing rate than pantoprazole 40 mg; pooled risk difference (2 studies) 14% (95% CI 7 to 20)
    - At 8 weeks, no difference was found in a single small study of patients with mild to moderate esophagitis.
- Lansoprazole 30 mg (2 studies) and esomeprazole 20 mg (1 study) were no different to omeprazole 20 mg at 4 or 8 weeks.

Prevention of relapse in patients with erosive esophagitis

- For maintenance of healed esophagitis, there was good evidence that no difference exists between omeprazole, lansoprazole, and rabeprazole. The longest study (over 5 years) compared omeprazole with rabeprazole.
- Two 6-month studies found lower relapse rates for esomeprazole 20 mg than for lansoprazole 15 mg or pantoprazole 20 mg.
- No difference was found between esomeprazole 20 mg and pantoprazole 20 mg in combined symptomatic and endoscopic remission rates after 6 months.

Symptom relief in patients with nonerosive gastroesophageal reflux disease or presumptively treated symptoms of gastroesophageal reflux disease

- Three head-to-head trials in patients with gastroesophageal reflux disease but without erosive esophagitis on endoscopy found no difference between esomeprazole 20 mg and omeprazole 20 mg, pantoprazole 20 mg, or rabeprazole 10 mg. These studies used different outcome measures.
- Limited indirect evidence from placebo-controlled and active-control trials suggested similar efficacy for heartburn resolution and complete symptom relief for all 5 proton pump inhibitors.

Evidence in children

- There were no direct comparisons of proton pump inhibitors for reflux esophagitis in children. A fair-quality placebo-controlled trial in infants did not find omeprazole to be superior to placebo in controlling symptoms or acid-exposure time.

Detailed Assessment

Erosive esophagitis

We identified 31 randomized controlled trials comparing 2 or more proton pump inhibitors in patients with gastroesophageal reflux disease with endoscopically-proven erosive esophagitis (Evidence Table 1).[4-6, 10-38] Two publications are supplemented with additional data provided by the manufacturer.[4, 5] Most studies used omeprazole. No study of omeprazole in combination with sodium bicarbonate met inclusion criteria. The scales used to grade esophagitis in these studies are described in Appendix E.

In most studies of proton pump inhibitors, patients who have esophagitis before treatment undergo another endoscopy for assessment of healing 4 or 8 weeks after starting treatment. There is no evidence that rate of esophageal healing after 4 or 8 weeks of treatment is associated with risk of stricture or esophageal cancer in the long run. As distinct from symptom relief, the benefit of quicker esophageal healing is also uncertain.

The clinical importance of small differences in healing rates at 4 or 8 weeks is not known. In addition, patients who have clinically significant improvements but who are not completely healed (for example, patients whose esophagitis improves from LA classification scale grade D to grade B) are considered unhealed. Studies do not report the esophagitis grade for patients “not healed” at follow-up.

Resolution of symptoms

Five head-to-head comparisons of proton pump inhibitors measured symptom relief as a primary outcome, [10, 11, 13, 16, 37] and 14 reported symptoms as a secondary outcome.[4, 5, 12, 14, 15, 17, 21-26, 30, 32, 35] Symptoms in these studies were assessed through patient diaries, investigator-elicited reports, or both.

Sixteen head-to-head trials reported the proportion of patients with resolution of symptoms at 4 weeks.[4, 5, 10, 12-14, 16, 17, 20, 23, 24, 26, 27, 29, 33, 36] We performed a random-effects meta-analysis of data from these studies to determine an estimate of the proportion who were symptom-free at 4 weeks for each drug. Results are shown in Table 2. Proportions ranged from 65% to 77%, and 95% confidence intervals overlapped, indicating the drugs are similarly efficacious for resolution of symptoms at 4 weeks.

A systematic review of most of these trials, with search dates through 2004, evaluated the proton pump inhibitors as a group and compared to one another.[39] This meta-analysis found omeprazole 20 mg daily to be inferior to esomeprazole 40 mg or lansoprazole 30 mg daily in heartburn relief at day 1, with relative risks of 0.78 (95% CI 0.71 to 0.85) and 0.82 (95% CI 0.75 to 0.88), respectively. Lansoprazole and esomeprazole were not found statistically different (relative risk 1.03; 95% CI 0.87 to 1.22). Our analysis includes more recently published trials.

Table 2. Symptom resolution in head-to-head trials in patients with erosive gastroesophageal reflux disease

Proton pump inhibitor and daily dose	Resolution of symptoms at 4 weeks (95% CI)	Reference number
Esomeprazole 40 mg	73% (65 to 82)	4, 5, 10, 12, 16, 20, 29
Lansoprazole 30 mg	70% (61 to 80)	4, 13-15, 23, 29
Omeprazole 20 mg	65% (54 to 76)	5, 12, 13, 16, 24, 26, 27
Omeprazole 40 mg	76% (65 to 87)	14, 17
Pantoprazole 20 mg	77% (70 to 84)	27
Pantoprazole 40 mg	72% (62 to 83)	10, 13, 17, 20, 23, 26
Rabeprazole 20 mg	69% (52 to 86)	24

Figure 2 shows risk differences in rates of symptom resolution at 4 weeks in these trials.[4, 5, 10, 12-14, 16, 17, 20, 23, 24, 26, 27, 29, 33, 36] In Table 3 we report the difference in symptom resolution for esomeprazole compared with other proton pump inhibitors. The pooled data on the comparison of esomeprazole 40 mg with omeprazole 20 mg significantly favored esomeprazole; for every 13 persons treated with esomeprazole 40 mg instead of omeprazole 20 mg, 1 additional patient would be symptom-free at 4 weeks in the esomeprazole group. The pooled data for comparison of esomeprazole 40 mg with either lansoprazole 30 mg or pantoprazole 40 mg did not indicate a significant difference between drugs.

Figure 2. Resolution of symptoms at 4 weeks in head-to-head trials of proton pump inhibitors

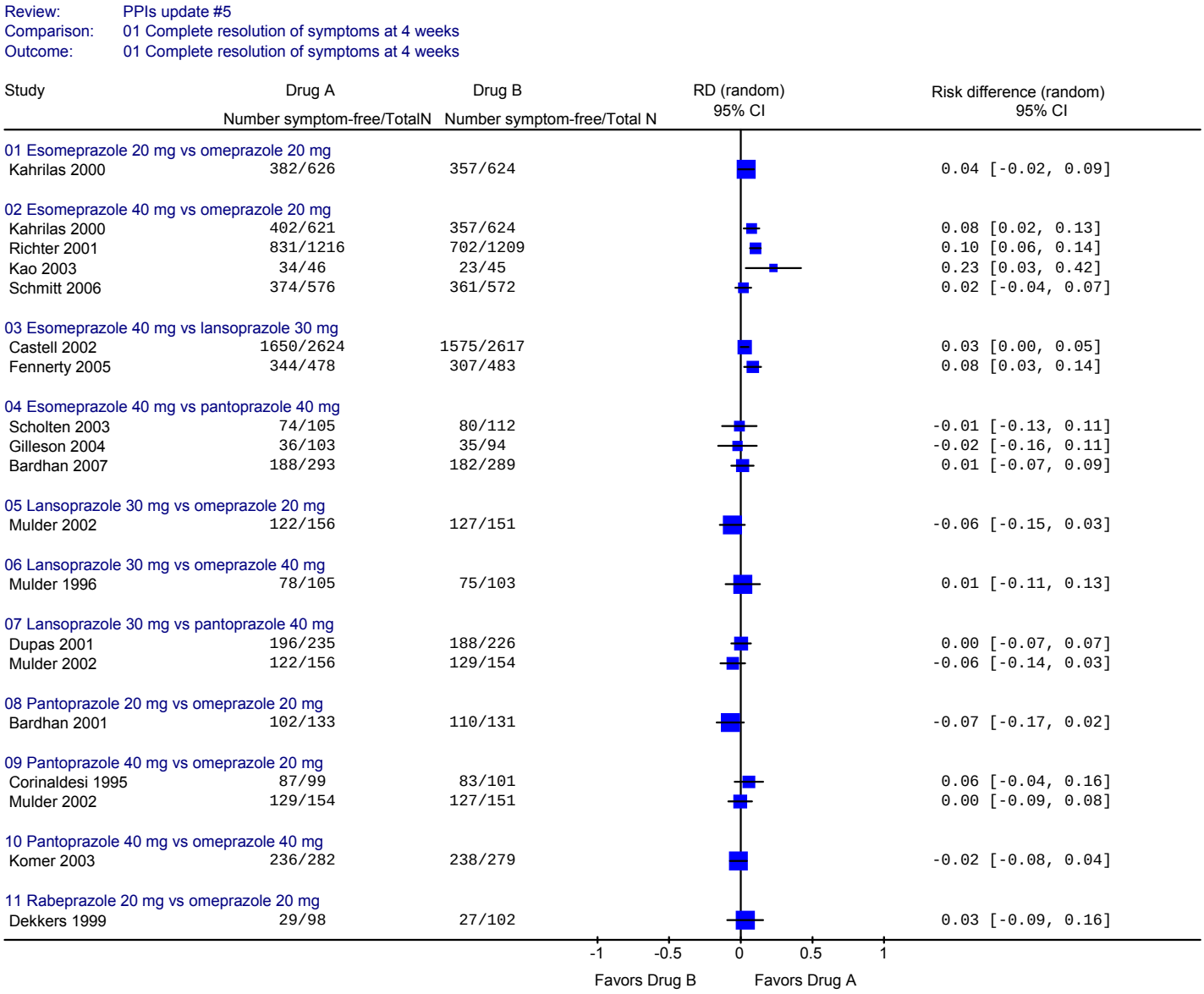


Table 3. Symptom resolution at 4 weeks in trials of esomeprazole compared with another proton pump inhibitor in erosive gastroesophageal reflux disease

Study	Portion of group with resolution of symptoms at 4 weeks	Risk difference (95% CI)	Pooled estimate
Esomeprazole 40 mg compared with omeprazole 20 mg			
Kahrilas 2000[5]	65% vs. 57%	8% (2 to 13)	**8% (3% to 13%) number needed to treat=13**
Kao 2003[16]	74% vs. 51%	23% (3 to 42)	
Richter 2001[12]	68% vs. 58%	10% (6 to 14)	
Schmitt 2006[36]	65% vs. 63%	2% (–4 to 7)	
Esomeprazole 40 mg compared with lansoprazole 30 mg			
Castell 2002[4]	63% vs. 60%	3% (0 to 5)	**5% (0% to 9%)**
Fennerty 2005[29] (ITT[a])	69% vs. 61%	8% (2 to 14)	
Esomeprazole 40 mg compared with pantoprazole 40 mg			
Bardhan 2007[33]	64% vs. 63%	1% (–7 to 9)	**0% (–6% to 6%)**
Gillessen 2004[20]	35% vs. 37%	–2% (–16 to 11)	
Sholten 2003[10]	70% vs. 71%	–1% (–13 to 11)	

[a] Intention-to-treat analysis performed for this report.

A single study reported resolution of symptoms after 1 week of therapy,[32] finding rabeprazole 20 mg daily superior to omeprazole 20 mg daily (resolution in 27.9% of patients compared with 16.6%, *P*=0.0013 as calculated from number randomized and using chi square analysis).

A head-to-head trial of pantoprazole 40 mg compared with esomeprazole 40 mg used the ReQuest Score to assess symptoms.[35] ReQuest is a validated self-assessment scale used to measure symptoms in erosive and nonerosive gastroesophageal reflux disease. Measured on the last 3 days of a 4-week treatment period, the median ReQuest-GI score in patients taking pantoprazole was found to be non-inferior to the median score in patients taking esomeprazole.

Time to relief of symptoms

Fourteen studies reported the time to resolution of symptoms (no heartburn). This outcome usually was reported as the percentage of patients with symptom resolution by a given time point, such as 1 day or 7 days), the median number of days to resolution, or both. One study reported this outcome as the number of days needed for 50% and 75% of patients to achieve resolution of symptoms.[10]

Another measure was the time to sustained resolution of heartburn, defined as the first of 7 consecutive days without heartburn. This outcome was used only in studies funded by the maker of esomeprazole, so it is not possible to compare this outcome with studies funded by others.

Esomeprazole compared with omeprazole. In 4 studies that compared esomeprazole 40 mg with omeprazole 20 mg, the median number of days to the *first* resolution of symptoms was similar; however, the median number of days to sustained resolution of symptoms favored esomeprazole in the 2 studies reporting this measure (Table 4).[5, 12, 16] More patients taking esomeprazole 40 mg reached *first* of resolution of symptoms by day 1 and day 7 in absolute proportions than patients taking omeprazole 20 mg. These findings were statistically significant in 1 study,[12] nonsignificant in 2 others,[16, 31] and not assessed in the fourth.[5] The time to *sustained* resolution of heartburn was statistically superior with esomeprazole 40 mg compared to omeprazole 20 mg at day 14 in 2 studies.[12, 16] The differences at other time points were mixed or not statistically assessed. One of these studies used a tablet formulation of esomeprazole that is not available in the US or Canada.[31]

In a comparison of esomeprazole 20 mg with omeprazole 20 mg,[5] a higher proportion of omeprazole patients started 7 consecutive days without heartburn at day 1; esomeprazole had a higher proportion of patients with sustained relief by day 28. Neither comparison was statistically significant. The median number of days to sustained resolution was similar. This pattern was also seen in the time to first resolution of symptoms.

Table 4. Time to symptom relief in trials comparing esomeprazole with omeprazole in erosive gastroesophageal reflux disease

Study	Proportion with first resolution of heartburn		Proportion that has begun sustained resolution of heartburn (7 consecutive days)			
Esomeprazole 20 mg compared with omeprazole 20 mg						
Kahrilas 2000	Day 1: 38% vs. 37% *P*=0.76	Day 7: 81% vs. 80% *P*=0.81	Day 1: 22% vs. 23% *P*=0.60		Day 28: 70% vs. 67% *P*=0.18	
Esomeprazole 40 mg compared with omeprazole 20 mg						
Kahrilas 2000	**Day 1: 47% vs. 37% *P*=0.0006**	Day 7: 83% vs. 80% *P*=0.12	**Day 1: 30% vs. 23% *P*=0.01**		**Day 28: 74% vs. 67% *P*=0.003**	
Kao 2003	Day 1: 28% vs. 26% NS	Before day 7: 56% vs. 56% NS	Day 7: 15% vs. 15.6% NS	Day 14: 50% vs. 20% *P*<0.05	Day 21: 72% vs. 40% *P*<0.01	Day 28: 74% vs. 51% *P*<0.05
Richter 2001	**Day 1: 45% vs. 32% *P*≤0.0005**	**Day 7: 86% vs. 82% *P*≤0.0005**	Day 1: 29% vs. 20% *P*≤0.0005		Day 14: 68% vs. 63% *P*≤0.0005	
Chen 2005	Day 1: 77.3% vs. 65% NS		Not reported			

Esomeprazole compared with lansoprazole. In 3 studies comparing esomeprazole 40 mg with lansoprazole 30 mg, results were mixed and outcomes were reported differently (Table 4). Overall, results did not favor one drug over another.

Esomeprazole compared with pantoprazole. The 2 trials comparing esomeprazole with pantoprazole reported time to symptom resolution differently and found conflicting results. In 1

trial comparing esomeprazole 40 mg with pantoprazole 40 mg, 4% more esomeprazole patients began sustained resolution of heartburn (7 consecutive days) after 1 day of treatment: 24% compared with 20% (*P* value not reported).[30] The median time to sustained resolution was 6 days with esomeprazole, compared with 8 days (*P*<0.001). Based on this same life-table analysis, the Cumulative proportion of patients reporting sustained resolution of heartburn was 78% with esomeprazole and 77% with pantoprazole, again a small difference but found to be statistically significant (*P*<0.001). A second trial comparing esomeprazole 40 mg with pantoprazole 40 mg looked at the number of days required for relief of heartburn in 50% and 75% of patients.[10] In both groups, 50% of patients had no heartburn after 2 days. But it took 3 days for 75% of the pantoprazole group to be relieved of symptoms and 8 days for the esomeprazole group. Confidence intervals overlapped, (95% CI for pantoprazole, 2 to 7 days; for esomeprazole, 3 to14 days) suggesting a significant difference between the drugs is unlikely but not proven.

Lansoprazole compared with omeprazole. Three studies reported time to relief of heartburn with lansoprazole compared with omeprazole.[14, 15, 25] Although lansoprazole improved some symptoms more quickly, there was no strong or consistent pattern suggesting that lansoprazole provides faster symptom relief than omeprazole. Time to sustained resolution of heartburn (defined as 3 consecutive days without heartburn) was measured in 1 study and was similar for the drugs (median 3 days for both drugs, *P*=0.285).[14] In another study, daytime and nighttime heartburn were reported separately.[25] After 1 day of treatment, more lansoprazole patients were free of day heartburn (48.7% compared with 37.6%, *P*<0.05) and night heartburn (62% compared with 52%, *P*<0.05). The third comparison of these drugs used a visual analogue scale to measure heartburn and reported the time to relief only for daytime heartburn.[15] After 3 days, there was a significant decrease in symptom score in lansoprazole patients (–20.2 compared with –15.3, *P*=0.05); the difference was not significant after 7 days (scores not reported).

Rabeprazole compared with omeprazole. One study reported similar mean time to complete relief of heartburn for rabeprazole and omeprazole 20 mg daily (7 and 8 days, respectively).[32] A second study reported median time to achieve heartburn control, defined as the first day heartburn score was below 3 on a 5-point Likert scale.[34] The median time to heartburn control was 1.5 days for both rabeprazole and omeprazole (*P*<0.43).

Healing of esophagitis

All the proton pump inhibitors allowed esophagitis to heal. Healing rates at 4 weeks ranged from 49% to 91% and at 8 weeks ranged from 71% to 99% (see Evidence Table 1). One small, fair-quality study conducted at a single center in China had a lower 8-week healing rate than other studies (64% for esomeprazole 40 mg, 45.5% for omeprazole 20 mg).[31]

To estimate healing rates for each drug, we pooled data from head-to-head trials, using a random-effects model to control for the effect of the study. Table 5 shows results of this analysis. (Note that data for lansoprazole 15 mg, pantoprazole 20 mg, and rabeprazole 10 mg are available from only 1 study). Healing rates were similar and confidence intervals overlapped, indicating no significant differences between proton pump inhibitors.

Table 5. Pooled estimates of healing rates for esophagitis in head-to-head trials of proton pump inhibitors

Drug	Proportion of group whose esophagitis has healed at 4 weeks (95% CI)	Proportion of group whose esophagitis has healed at 8 weeks (95% CI)
Esomeprazole 20 mg	73% (66-79)[5, 6]	87% (84-91)[5, 6]
Esomeprazole 40 mg	78% (73-83)[4, 5, 12, 20, 29, 30, 36, 38]	90% (88-92)[4, 5, 12, 18, 20, 29-31, 38]
Lansoprazole 15 mg	63% (52-73)[25]	73% (63-82)[25]
Lansoprazole 30 mg	73% (67-79)[4, 14, 15, 21, 23, 25, 29]	86% (83-90)[4, 14, 15, 18, 21, 23, 25, 29]
Omeprazole 20 mg	70% (64-76)[5, 6, 12, 15, 21, 22, 25-27, 38]	85% (81-88)[5, 6, 12, 15, 21, 22, 25-27, 31, 38]
Omeprazole 40 mg	68% (59-78)[14, 17]	87% (76-99)[14]
Pantoprazole 20 mg	67% (54-81)[27]	77% (65-88)[27]
Pantoprazole 40 mg	71% (65-78)[17, 20, 23, 26, 30]	89% (86-92)[20, 23, 26, 30]
Rabeprazole 10 mg	65% (47-83)[22]	84% (71-96)[22]
Rabeprazole 20 mg	69% (59-79)[22, 40]	82% (76-89)[22, 40]

Data from the cited studies were pooled using a random-effect model.

We also calculated the risk difference for healing in head-to-head comparisons. Figures 3 and 4 show the differences in healing rates at 4 and/or 8 weeks for the 23 trials that provided the number healed/total patients.[4-6, 12, 14, 15, 17, 18, 20-23, 25-27, 29-33, 36, 37] Seven head-to-head trials are not represented in Figures 3 and 4: Three studies (2 comparing rabeprazole with omeprazole, 1 comparing omeprazole with both lansoprazole and rabeprazole)[19, 28, 41] did not provide number healed/total and 4 trials[10, 11, 13, 16] reported only symptom relief, not esophagitis healing. For 1 trial comparing rabeprazole 20 mg with omeprazole 20 mg the figures show calculated intention-to-treat numbers, rather than those from the article, which are not intention-to-treat.[32]

Although some published studies present results according to life-table analysis, only crude rates are included in Figure 3. For published studies that do not provide crude rates, we requested and received these data from the manufacturer. Results of life-table analyses cannot be directly compared with crude rates reported in other studies, and using life-table analysis may overestimate results by excluding patients who are lost to follow-up or have withdrawn from the study.

Omeprazole 20 mg, the first proton pump inhibitor to be marketed, was the proton pump inhibitor used most often in head-to-head trials. Table 6 summarizes the risk differences in healing rate in 9 trials[12, 15, 21, 22, 25-27, 31, 36] that compared daily omeprazole 20 mg with another proton pump inhibitor. Risk difference at 4 and 8 weeks was significant in only 1 comparison, esomeprazole 40 mg compared with omeprazole 20 mg. The pooled risk difference for 3 studies at 4 weeks was 8% and for 4 studies at 8 weeks was 6%. These risk differences translate to numbers needed to treat to heal 1 additional patient of 13 at 4 weeks and 17 at 8 weeks.

Figure 3. Esophagitis healing at 4 weeks in head-to-head trials of proton pump inhibitors

Review: PPIs update #5
Comparison: 02 Esophagitis healing at 4 weeks
Outcome: 01 Esophagitis healing at 4 weeks

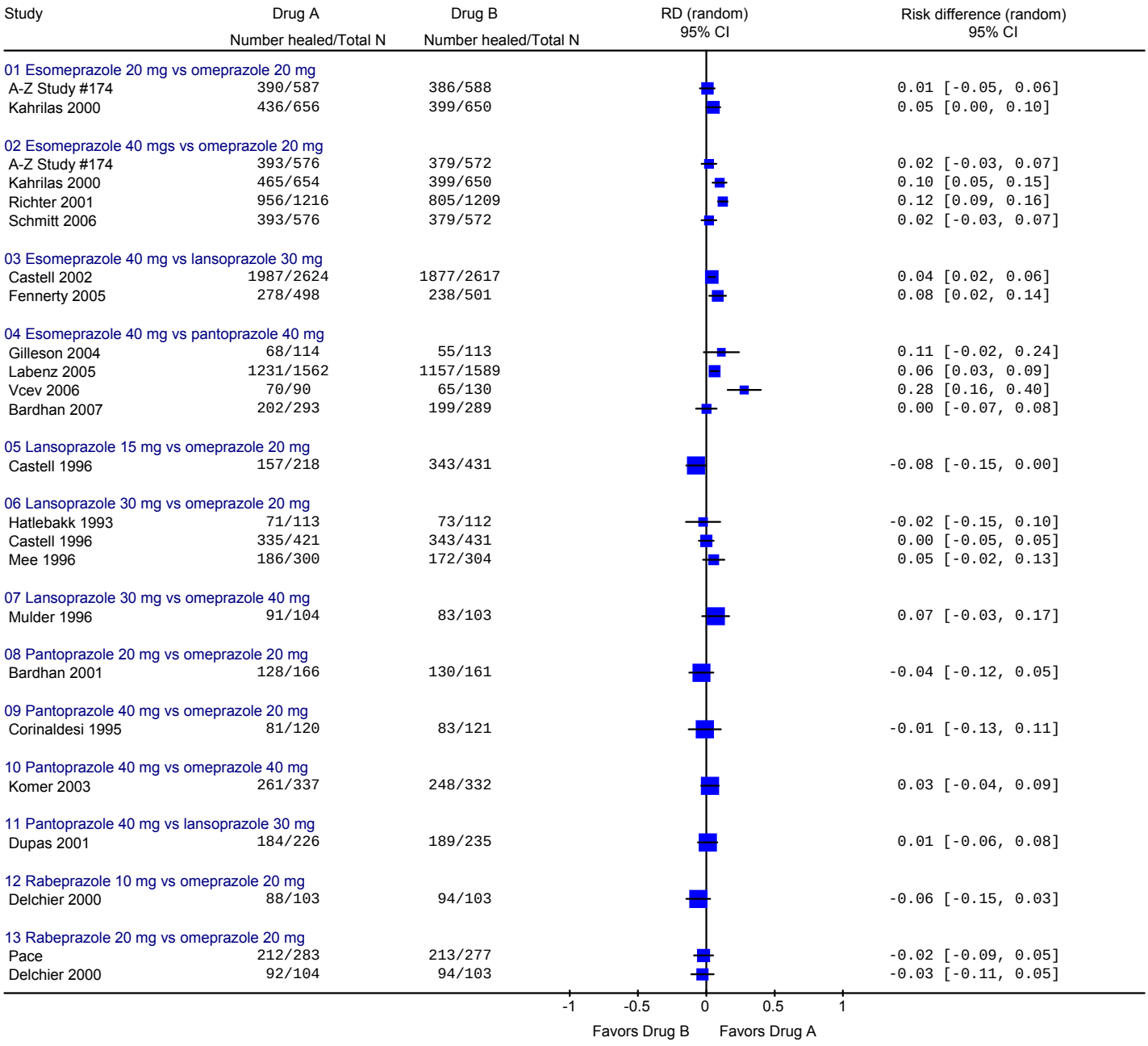


Figure 4. Esophagitis healing at 8 weeks in head-to-head trials of proton pump inhibitors

Review: PPIs update #5
Comparison: 03 Esophagitis healing at 8 weeks
Outcome: 01 Esophagitis healing at 8 weeks

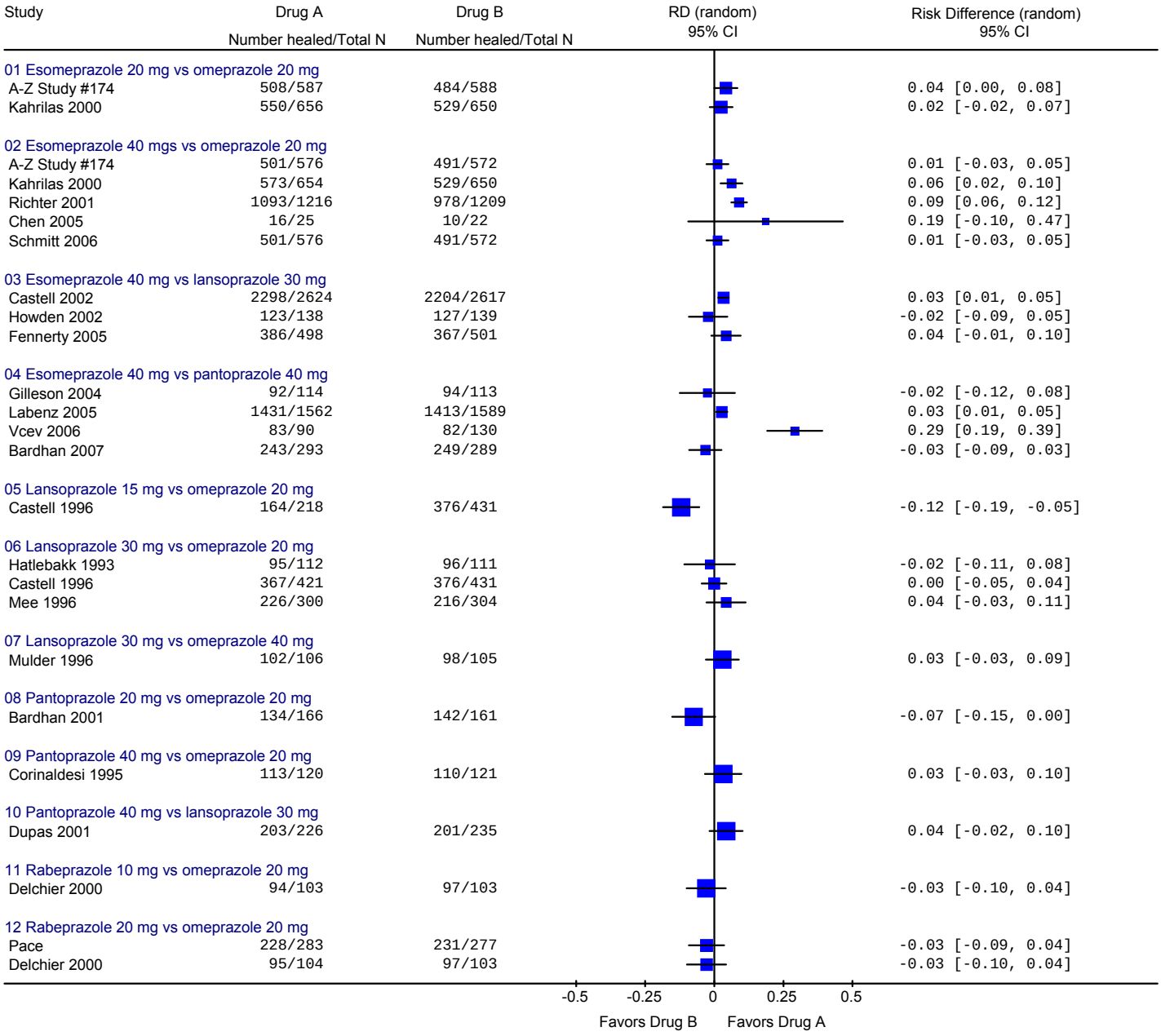


Table 6. Risk differences in healing of esophagitis in trials of omeprazole 20 mg compared with another proton pump inhibitor

Drug, daily dose	Risk difference[a] at 4 weeks in comparison with omeprazole (95% CI)	Risk difference[a] at 8 weeks in comparison with omeprazole (95% CI)
Esomeprazole 20 mg	3% (–1 to 7)[5, 6]	3% (0 to 6)[5, 6]
Esomeprazole 40 mg	7% (1 to 12), pooled[5, 12, 36, 38 36] **number needed to treat = 14**	5% (1 to 9), pooled[5, 12, 31, 36, 38] **number needed to treat = 20**
Lansoprazole 30 mg	2% (–3 to 6), pooled [15, 21, 25]	1% (–2 to –5), pooled [15, 21, 25]
Pantoprazole 20 mg	–4% (–12 to 5)[27]	–7% (–15 to 0)[27]
Pantoprazole 40 mg	–1% (–13 to 11)[26]	3% (–3 to 10)[26]
Rabeprazole 10 mg	–6% (–15 to 3)[22]	–3% (–10 to 4)[22]
Rabeprazole 20 mg	–2% (–8 to 3)[22, 32]	–3% (–8 to 2)[22, 32]

[a] Risk difference was calculated as the difference between the percent of the group on the test proton pump inhibitor in which esophagitis healed and the percent of the group on omeprazole 20 mg daily in which esophagitis healed.

Two published trials comparing esomeprazole 40 mg with omeprazole 20 mg found a statistically significantly higher healing rate in the esomeprazole group.[5, 12] Two others[36, 38] found no difference between groups at 4 and 8 weeks. A small study (N=48) not included in Table 5 found a higher healing rate for esomeprazole at 8 weeks (64% compared with 46%), but the difference was not statistically significant.[31] The study may not have had sufficient power to detect a difference between treatment groups; no power calculation was reported. This study did not measure 4-week healing rates.

The pooled risk difference for 4 studies at 4 weeks was 7% and for 5 studies at 8 weeks was 5%, favoring esomeprazole (see Table 6). This translates to a number needed to treat with esomeprazole to heal 1 additional patient at 4 weeks of 14, and a number needed to treat at 8 weeks of 20.

Three studies compared esomeprazole 40 mg with lansoprazole 30 mg.[4, 18, 29] In a large, good-quality trial in 5241 patients at multiple centers in the United States,[4] healing rates were higher in the esomeprazole group at 4 and 8 weeks. A smaller, fair-quality trial[18] in patients with mostly mild to moderate esophagitis found the drugs to have equivalent healing rates at 8 weeks; results at 4 weeks were also similar between drugs. The third study, rated good quality,[29] was conducted in patients with moderate to severe esophagitis. At 4 weeks, the esomeprazole group had a higher healing rate, but at 8 weeks the difference was not significant.

Pooled estimates show that with esomeprazole, healing rate is higher by 5% at 4 weeks and by 3% at 8 weeks (Table 6). With a random-effects analysis the difference at 8 weeks is not significant, but in fixed-effects analysis, the difference is significant (see table 6). The fixed-effect estimates of risk difference correspond to a number of patients needed to treat with esomeprazole instead of lansoprazole to heal 1 additional patient at 4 weeks equal to 20 and at 8 weeks equal to 33.

Table 7. Risk differences in healing of esophagitis in head-to-head trials of esomeprazole 40 mg compared with lansoprazole 30 mg

Study	Difference in healing[a] at 4 weeks (95% CI)	Difference in healing[a] at 8 weeks (95% CI)
Castell 2002[4]	4% (2 to 6)	3% (1 to 5)
Fennerty 2005[29]	8% (2 to 14)	4% (–1 to 10)
Howden 2002[18]	Not reported	–2% (–9 to 5)
Pooled estimates		
Random effects	5% (1 to 9)	3% (0 to 5)
Fixed effects	**5% (2 to 7)** **number needed to treat = 20**	**3% (1 to 5)** **number needed to treat = 33**

[a] Difference in healing was calculated as the difference between the esomeprazole group and the lansoprazole group in the percent in which esophagitis was healed.

Four trials compared esomeprazole 40 mg with pantoprazole 40 mg.[20, 30, 33, 37] Two studies find esomeprazole superior, while 2 do not. One[30] large study (N=3171) found that healing at 4 weeks was 6% higher in the esomeprazole group (95% CI 3 to 9). At 8 weeks, the difference was smaller but statistically significant (risk difference, 3%; 95% CI 1 to 5). We rated this study fair quality. A much smaller study (N=180) was also rated fair to poor because numbers of patients enrolled and analyzed in tables did not match the numbers discussed in the text (apparently a typographical error was made in Table 1), the study was apparently open-label, and no details on randomization or allocation concealment procedures were given.[37] This study also found esomeprazole 40 mg to have significantly higher rates of healing at 4 weeks (78% compared with 72%; $P<0.05$). Rates at 8 weeks were not statistically significantly different (92% compared with 91%). No patients with Grade D esophagitis were enrolled in this study, although they were not excluded

Two studies (N=227 and 581) found no differences in healing rates between the drugs[20, 33] at early time points (4 to 6 weeks in 1 study, 4 weeks in the other) or later time points (8 to 10 weeks in 1 study, 8 and 12 weeks in the other). The smaller of these studies included only patients with Grade B or C esophagitis.[20]

The 2 largest of these studies also examined the impact of *Helicobacter pylori* status on healing rates with the 2 drugs. One found that healing rates with esomeprazole were not different based on *Helicobacter pylori* status, but that *Helicobacter pylori* negative patients had lower healing rates with pantoprazole compared to those who were *Helicobacter pylori* positive.[30] The other study, however did not find any associated differences in healing rate, symptom relief or 'complete remission' when using intention to treat analyses.[33]

The largest study[30] reports only life-table analysis results, while the other studies report raw rates of number of patients healed. However, data on the crude rates of healing were provided by AstraZeneca through public comment on this report; the data used in the analysis below for this study are not published data. Using these data to conduct a pooled analysis of the 3 studies that included patients with all grades of esophagitis indicates that esomeprazole 40 mg is superior to pantoprazole 40 mg in rates of patients with healed erosions at 4 weeks, but not at 8 weeks (Table 8 below). Sensitivity analysis including the fourth study which included only patients with Grades B and C esophagitis,[20] or only the 2 highest quality studies, did not change these results.[30, 33]

Table 8. Risk differences in healing of esophagitis in trials of esomeprazole 40 mg compared with another proton pump inhibitor

Drug, daily dose	Risk difference[a] at 4 weeks in comparison with esomeprazole 40 mg (95% CI)	Risk difference[a] at 8 weeks in comparison with esomeprazole 40 mg (95% CI)
Lansoprazole 30 mg[4, 18, 29]		
Pooled estimates Random effects	5% (1% to 9%)	3% (0% to 5%)
Fixed effects	**5% (2% to 7%)** **number needed to treat = 20**	**3% (1% to 5%)** **number needed to treat = 33**
Pantoprazole 40 mg[20, 30, 33, 37]		
Pooled estimates Random effects	5% (2% to 8%) **number needed to treat = 20**	1% (-3% to 5%)
Fixed effects	5% (2% to 8%) **number needed to treat = 20**	2% (-0.2% to 4%)

[a] Risk difference was calculated as the difference between the percent of the group on the test proton pump inhibitor in which esophagitis healed and the percent of the group on esomeprazole 40 mg daily in which esophagitis healed.

Analysis of healing rates by baseline severity of esophagitis

Nineteen head-to-head trials reported information about esophagitis healing rates by baseline severity of esophagitis.[4-6, 12-15, 18-23, 25, 27, 29, 30, 37, 38] These results are shown in Evidence Table 1. Ten trials stratify by baseline severity the ratio of number of patients with healed esophagitis to total number patients (Figures 5 and 6).[4-6, 12, 15, 25, 29, 30, 37, 38] To estimate healing rate for each drug at 4 and 8 weeks for patients with moderate to severe esophagitis (that is, grades C-D or 3-4; see Appendix E for grading scales), we conducted a random-effects meta-analysis of data from these 9 studies[4-6, 12, 15, 25, 29, 30, 38] (Table 9). An additional study[18] reports a combined outcome of improved by 2 grades or healed; those data were not included in the meta-analysis.

Figure 5. Healing of moderate to severe esophagitis at 4 weeks in head-to-head trials of proton pump inhibitors

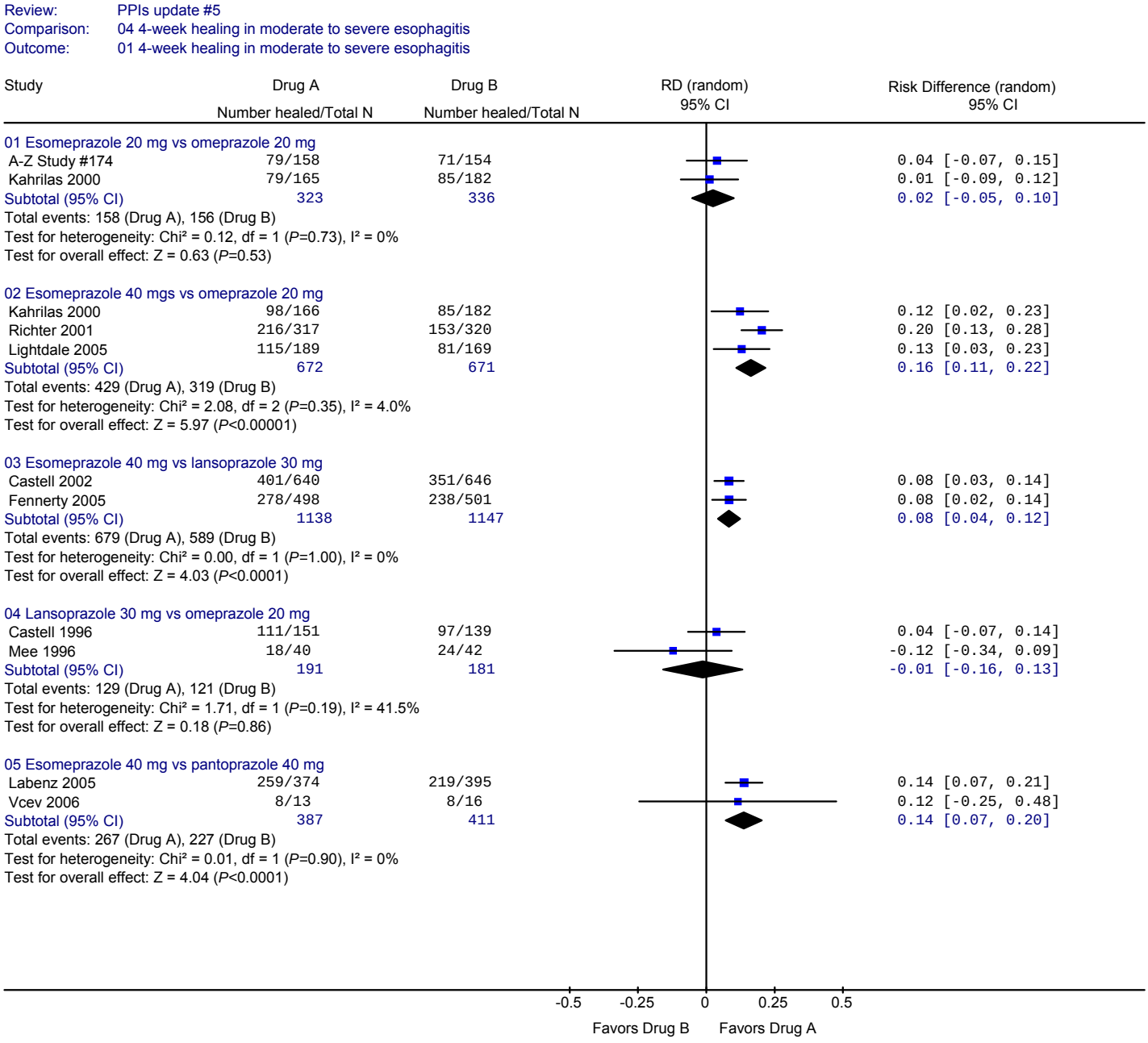


Figure 6. Healing of moderate to severe esophagitis at 8 weeks in head-to-head trials of proton pump inhibitors

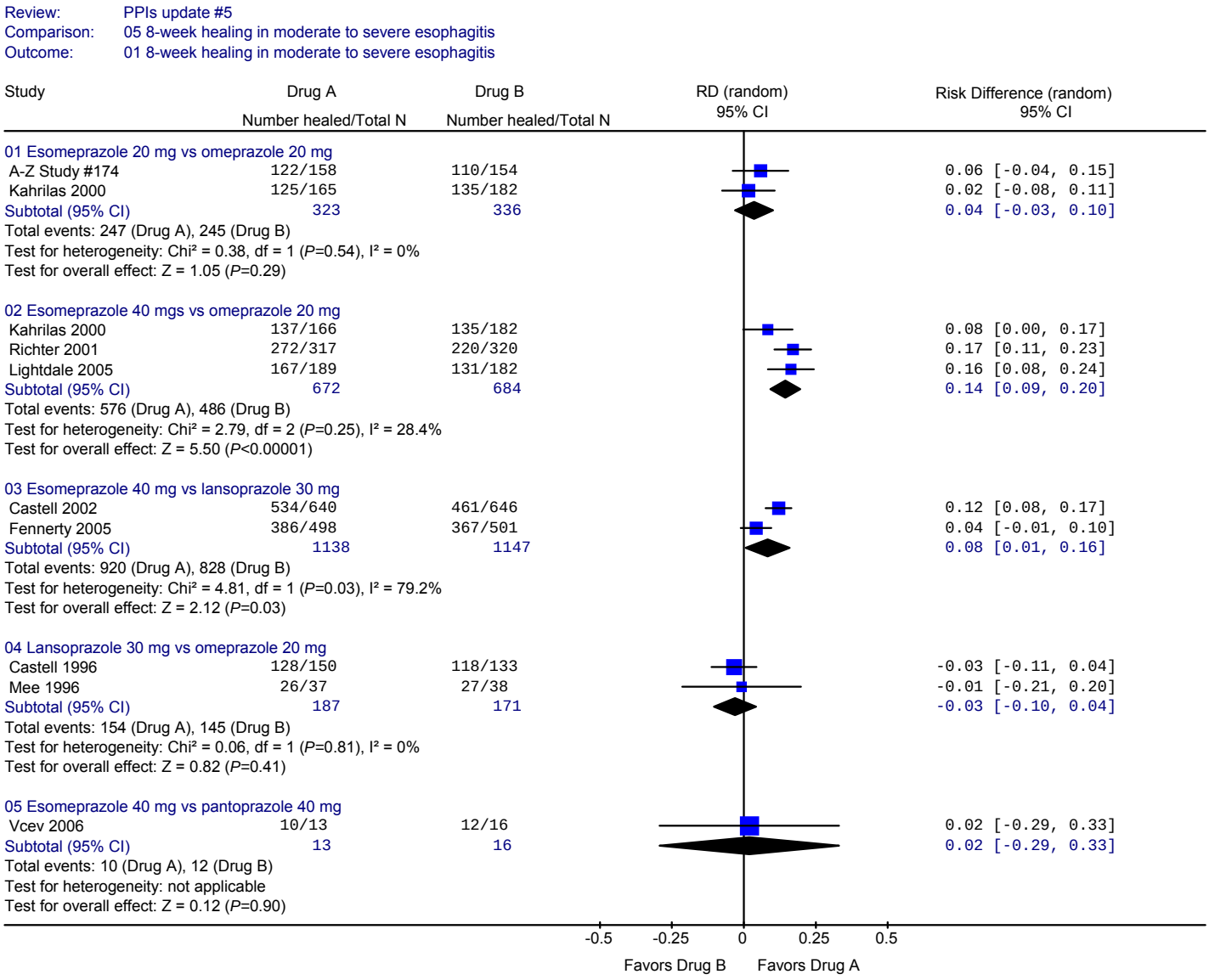


Table 9. Estimated healing rates in patients with moderate to severe esophagitis at baseline

Drug and daily dose	Percent patients with healed esophagitis at 4 weeks (95% CI)	Percent patients with healed esophagitis at 8 weeks (95% CI)
Esomeprazole 20 mg	49% (37-61)[5, 6]	77% (70-85)[5, 6]
Esomeprazole 40 mg	64% (57-71)[4, 5, 12, 29, 30, 38]	85% (81-89)[4, 5, 12, 29, 38]
Lansoprazole 30 mg	56% (48-64)[4, 15, 25, 29]	77% (71-82)[4, 15, 25, 29]
Omeprazole 20 mg	52% (45-59)[5, 6, 12, 15, 25, 38]	74% (68-80)[5, 6, 12, 15, 25, 38]

Esomeprazole compared with omeprazole. Four studies comparing daily esomeprazole 40 mg with omeprazole 20 mg[5, 12, 36, 38] reported healing rate in patients with moderate to severe esophagitis at baseline (Figures 5 and 6). The pooled risk difference at 4 weeks was 16% (95% CI 11 to 22) and at 8 weeks was 13% (95% CI 9 to 17).

In 2 studies comparing esomeprazole 20 mg with omeprazole 20 mg[5, 6] there was no difference in healing rate at 4 weeks (pooled risk difference 2%; 95% CI –5 to 10) or 8 weeks (pooled risk difference 4%; 95% CI –3 to 10). Estimates of healing rates with esomeprazole 20 mg were similar to omeprazole 20 mg (see Table 7). There were no comparisons of esomeprazole (any dose) with omeprazole 40 mg.

Esomeprazole compared with lansoprazole. Two studies comparing esomeprazole 40 mg with lansoprazole 30 mg reported healing rates in patients with moderate to severe esophagitis at baseline.[4, 29] The pooled risk difference at 4 weeks was 8% (95%, CI 4 to12) and at 8 weeks was 9% (95% CI 5 to 12). These correspond to a number needed to treat of 13 at 4 weeks and 11 at 8 weeks.

A third study, published by the maker of lansoprazole, reported only the combined outcome of healing or improvement of at least 2 grades in the subgroup of patients with moderate to severe esophagitis.[18] In this small (N=109) subanalysis lansoprazole had a statistically nonsignificant higher rate of healing/improvement at 8 weeks (10%; 95% CI –2 to 22); results at 4 weeks were not reported.

Esomeprazole compared with pantoprazole. In 1 study patients with moderate (Grade C) esophagitis at baseline who were taking pantoprazole 40 mg had a higher healing rate at "later" time points (8 to 10 weeks) than patients on esomeprazole 40 mg (67% compared with 45%).[20] Esophagitis in 100% of patients with Grade C esophagitis on pantoprazole and 91% of patients on esomeprazole improved by 1 or 2 grades (to Grade B or A) by the final visit (10 weeks). Rates at 4 weeks are not reported, and no patients with Grade D esophagitis were enrolled.

In 2 trials of esomeprazole 40 mg compared with pantoprazole 40 mg in patients with moderate to severe esophagitis, there was a 14% risk difference favoring esomeprazole after 4 weeks (95% CI 7 to 21).[30, 37] At 8 weeks, there was no difference between the drugs in healing rate, although the 1 study that reported this outcome was small (N=29). [37]

Lansoprazole compared with omeprazole. Three studies comparing lansoprazole with omeprazole reported healing rate in patients with moderate to severe (Grades 3 and 4) esophagitis.[14, 15, 25] Two of these compared lansoprazole 30 mg with omeprazole 20 mg.[15, 25] There was no difference in healing rate at 4 weeks (pooled risk difference 1%; 95% CI –13 to 16) or 8 weeks (pooled risk difference 3%; 95% CI –4 to 10). The third study compared lansoprazole 30 mg with omeprazole 40 mg and reported healing rates as percentages only.[14] There was no significant difference between groups at 4 or 8 weeks. The distribution of the severity of esophagitis among patients in this study is not reported.

Systematic reviews of head-to-head trials in patients with erosive esophagitis

Seven recent systematic reviews have been published comparing proton pump inhibitors for healing of esophagitis and relief of gastroesophageal reflux disease symptoms.[42-48] Five of the 7 reviews included studies of esomeprazole, and all concluded that esomeprazole is superior to other proton pump inhibitors for gastroesophageal reflux disease, based on the same studies

included in this report.[43, 44, 46-48] One of these 3 concluded that the better healing rate in patients taking esomeprazole 40 mg than those taking omeprazole 20 mg or lansoprazole 30 mg is attributable to increased efficacy of esomeprazole in patients with more severe esophagitis.[46] Another of these reviews was designed to compare the efficacy of esomeprazole compared with lansoprazole; it concluded that esomeprazole provides an additional benefit of 5% at 4 weeks and 4% at 8 weeks compared with lansoprazole 30 mg.[48] Both of these reviews were funded by the manufacturer of esomeprazole. The third of these systematic reviews,[47] for which the funding source is not reported, concluded that esomeprazole 40 mg was superior to omeprazole 20 mg for esophagitis healing after 4 weeks (relative risk, 1.18; 95% CI 1.14 to 1.23), but that this result was due to the nonequivalent, higher dose of esomeprazole. There were no differences among the other proton pump inhibitors.

A Cochrane review of short term management of reflux esophagitis found focused on the proton pump inhibitors as a group, with minimal emphasis on comparing the drugs.[42] A systematic review conducted in 2001[45] found that lansoprazole, rabeprazole, and pantoprazole had efficacy similar to omeprazole for healing. No study of esomeprazole had been done at the time.

Indirect evidence

Comparisons of proton pump inhibitors across studies are difficult because patient populations and healing rates in control groups were dissimilar.

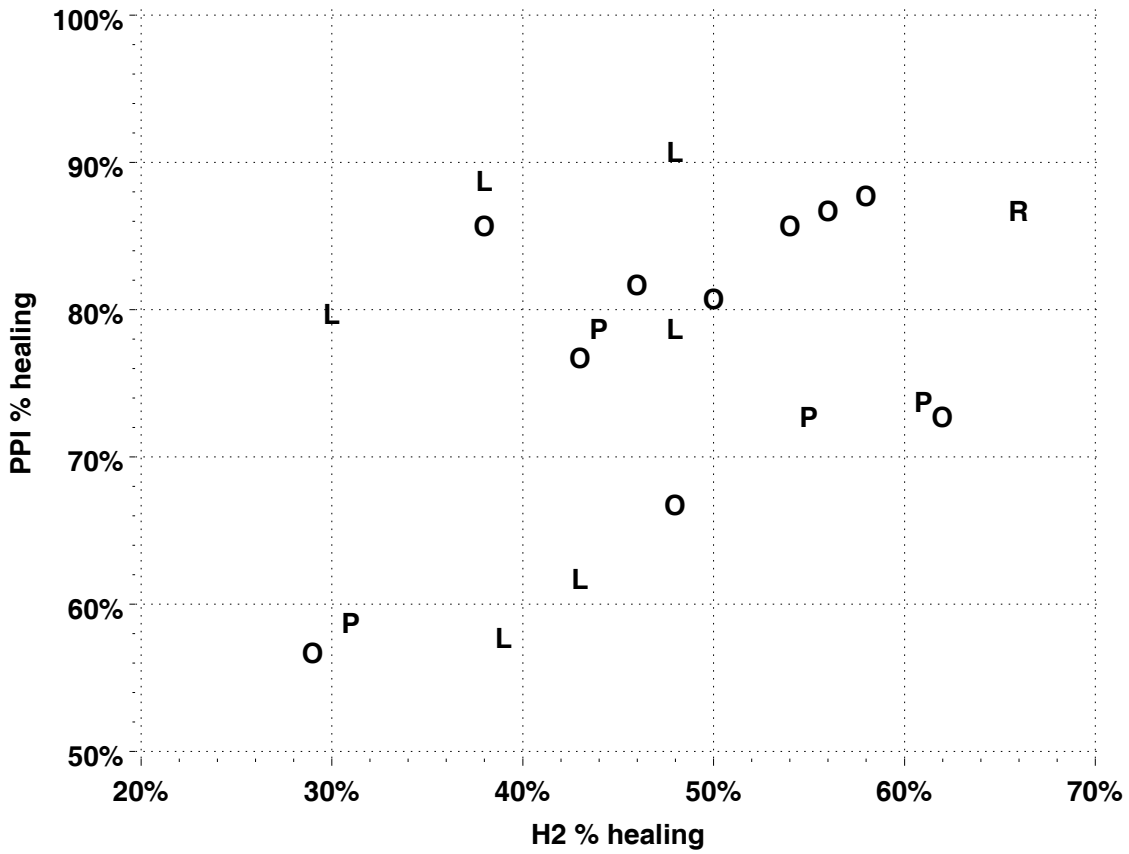
Esophagitis healing

In the systematic review mentioned above,[45] 4 proton pump inhibitors were better than ranitidine at healing esophagitis, but there were no differences among them. No study of esomeprazole was included.[45]

We reviewed 22 randomized controlled trials published through 2001 that compared a proton pump inhibitor with an H2 receptor antagonist for esophagitis healing. Figure 7 shows the rates of esophagitis healing at 8 weeks. These trials compared an H2 receptor antagonist with omeprazole (11 studies),[49-59] lansoprazole (5 studies),[60-64] pantoprazole (5 studies),[65-69] and rabeprazole (1 study).[70]

We did not create evidence tables of these studies or rate their quality, because after graphing their results we found no indication that the proton pump inhibitors differed. If an obvious difference in healing rates were seen in an individual study or studies, investigation of study quality would have been undertaken. In our meta-analysis, proton pump inhibitors were more effective at healing than H2 receptor antagonists, but there was no difference in healing rate among the proton pump inhibitors for any comparison. Healing rate ranged from 71.2% to 85.6%.

Figure 7. Esophagitis healing at 8 weeks in 22 randomized controlled trials comparing proton pump inhibitor with H2 receptor antagonist



Estimated healing rate	Mean percent patients with healed esophagitis (95% CI)
Lansoprazole	78.8% (69.7 to 86.4)
Omeprazole	79.3% (72.2 to 85.3)
Pantoprazole	71.2% (59.0 to 81.4)
Rabeprazole	85.6% (67.9 to 95.4)

Difference between proton pump inhibitors	Mean difference in percent patients with healed esophagitis (95% CI)
Lansoprazole vs. omeprazole	(–11.6 to 10.0)
Lansoprazole vs. pantoprazole	(–5.9 to 22.1)
Lansoprazole vs. rabeprazole	(–20.5 to 12.2)
Omeprazole vs. pantoprazole	(–4.3 to 21.7)
Omeprazole vs. rabeprazole	(–18.9 to 12.2)
Pantoprazole vs. rabeprazole	(–30.4 to 5.5)

Relief of symptoms

In 1 systematic review,[45] the pooled relative risk of studies that reported resolution of heartburn at 4 weeks was 1.02 (95% CI 0.94 to 1.11) for newer proton pump inhibitors (pantoprazole, rabeprazole, and lansoprazole) compared with omeprazole. For all 4 proton pump inhibitors compared with ranitidine the pooled relative risk was 1.53 (95% CI 1.37 to 1.72).

Prevention of relapse

Nine randomized controlled trials compared proton pump inhibitors in long-term (6 months or more) maintenance therapy to prevent relapse of esophagitis in patients with endoscopically-proven erosive gastroesophageal reflux disease (Evidence Table 4).[30, 71-78] Two of these found no differences in endoscopic or symptomatic relapse rates; 1 with lansoprazole compared with omeprazole after 48 weeks of treatment[71] and one with rabeprazole compared with omeprazole after 13 weeks, 26 weeks, 1 year, and 5 years.[77, 78]

Two studies compared esomeprazole 20 mg with pantoprazole 20 mg.[73, 76] In one,[76] patients took their proton pump inhibitor when needed, and in the other,[73] the proton pump inhibitor was taken daily. The study of daily treatment found no differences between treatment groups on the combined outcome of symptomatic and endoscopic remission.[73] The study of treatment on-demand measured efficacy using patient reports of the intensity of gastroesophageal reflux disease-related symptoms (0=none, 1=mild, 2=moderate, 3=severe). The mean intensity of heartburn was significantly higher (worse) in the esomeprazole group during the 6-month maintenance phase (1.32 for esomeprazole compared with 1.12 for pantoprazole; P=0.012). Pantoprazole patients took an average of 52.6 tablets (0.31 daily) and esomeprazole patients took an average of 59.9 tablets (0.36 daily); the difference between groups was not significant. Similarly, use of antacids as rescue medications was not statistically different between the groups (mean number of tablets in the esomeprazole group = 38, and in pantoprazole group = 53).

Two similar 6-month trials conducted by the same investigators compared esomeprazole 20 mg daily (a dose approved by the US Food and Drug Administration for healing or maintenance of erosive esophagitis) with lansoprazole 15 mg daily (approved dose for maintenance of healed erosive esophagitis)[75] or pantoprazole 20 mg daily (lower than the approved dose for maintenance of healed erosive esophagitis).[74] These studies randomized patients whose esophagitis had healed after 4 to 8 weeks of treatment and compared relapse rates at 6 months. According to life-table analysis, the esophagus of a higher proportion of patients in the esomeprazole groups remained healed over 6 months: 83% compared with 74% for esomeprazole compared with lansoprazole, respectively, and 87% compared with 74.9% for esomeprazole compared with pantoprazole. The authors also present data by baseline severity. The esophagus of more patients in the esomeprazole groups remained healed across all grades of disease severity in both studies. The efficacy of lansoprazole and pantoprazole decreased with increasing severity of disease in these studies. Esomeprazole showed lower rates of efficacy in preventing relapse in patients who started out with grade D esophagitis in only 1 study.[74] No crude rates or numbers of patients whose esophagitis remained healed were presented. Crude rates provide a more conservative estimate of effectiveness due to the manner in which dropouts are handled in life-table analyses. Because all patients enrolled in the study of esomeprazole and lansoprazole[75] had responded to esomeprazole for initial healing of esophagitis, the study may be biased towards esomeprazole. Both studies were funded by the manufacturer of esomeprazole and the publications were coauthored by representatives of the company.

A more recent study also compared daily esomeprazole 20 mg with lansoprazole 15 mg.[72] The primary outcome was remission, defined as no detectable erosive esophagitis and no study discontinuation due to reflux symptoms. After 6 months, remission was significantly greater in the esomeprazole group compared with the lansoprazole group (84.8% compared with 75.9%; P=0.0007). Remission rates were higher for esomeprazole in patients with either grade A and B or C and D esophagitis at baseline. Considering remission as measured by endoscopy alone, esomeprazole was superior to lansoprazole (86.9% compared with 77.8%; P=0.003). However, there were no significant differences between groups in the proportion of patients without symptoms at 6 months.

A shorter trial of 36 patients with severe (Savary-Miller Grade 4) esophagitis compared omeprazole, lansoprazole, and pantoprazole for the prevention of relapse at 4 weeks.[79] Before randomization, all patients were treated with omeprazole. Six patients did not heal after 6 to 8 weeks of omeprazole; the rest (83%) were randomized to omeprazole, lansoprazole, or pantoprazole. After 4 weeks, patients taking omeprazole had a lower rate of endoscopic relapse (10%) than those randomized to either lansoprazole (80%) or pantoprazole (70%). The relapse rates in the lansoprazole and pantoprazole groups were very high compared with other studies and, as in the study comparing esomeprazole with lansoprazole, discussed above, had a selection bias: All subjects had responded well to a study drug before enrollment in the maintenance phase.

Nonerosive and endoscopically unexamined gastroesophageal reflux disease

We identified 3 fair-quality head-to-head trials of proton pump inhibitors in short-term treatment of patients with nonerosive or empirically treated reflux disease. They compared esomeprazole with omeprazole,[80] rabeprazole,[81] or pantoprazole.[82] The 3 studies used different outcome measures, but all found esomeprazole to be similar in efficacy to the compared drug (Evidence Table 3). A fourth head-to-head trial (lansoprazole compared with omeprazole) included patients with erosive and nonerosive gastroesophageal reflux disease but did not separate results by these patient populations.[83] Three identically designed 4-week trials comparing omeprazole 20 mg and esomeprazole 20 mg and 40 mg were conducted simultaneously and were described in 1 publication.[80] There was no difference in the resolution of heartburn at 14 days (secondary outcome) or 28 days (primary outcome) between patients taking omeprazole 20 mg or esomeprazole 20 mg or 40 mg. At 2 weeks, proportions of patients with resolution ranged from 35% to 44%, and at 4 weeks ranged from 57% to 70%. Results for adequate control of symptoms were similar, with no significant differences between drugs.

A head-to-head trial comparing pantoprazole 20 mg with esomeprazole 20 mg measured time to first and sustained relief of symptoms.[84] This trial was designed to test for noninferiority of pantoprazole compared with esomeprazole. The noninferiority margin was set at –2 days for the primary outcome of time to first symptom relief (that is, a lower boundary of the 95% confidence interval greater than 2 days would indicate noninferiority). Symptom assessment was based on patient report using a validated questionnaire (ReQuest). The questionnaire includes items on the 7 dimensions of gastroesophageal reflux disease symptoms (general well-being, acid complaints, upper abdominal/stomach complaints, lower abdominal/digestive complaints, nausea, sleep disturbances, and other complaints). Results showed that pantoprazole was not inferior to esomeprazole for first and sustained relief of symptoms.

A 4-week trial comparing rabeprazole 10 mg with esomeprazole 20 mg was conducted in 134 patients in Singapore.[81] The primary outcome was time to first 24-hour period without

symptoms of heartburn or regurgitation. There was no difference between groups on this endpoint (for heartburn, 8.5 days for rabeprazole compared with 9.0 days for esomeprazole; for regurgitation, 6.0 days for rabeprazole compared with 7.5 days for esomeprazole; *P*=NS). There was also no significant difference between groups on secondary outcomes, including complete and satisfactory relief of heartburn symptoms at weeks 1 and 4, and symptom severity score in the first 5 days.

A good-quality Cochrane systematic review of literature through 2003 addressed the efficacy of proton pump inhibitors, H2 receptor antagonists, and prokinetics in adults with endoscopically verified nonerosive or empirically treated symptoms of reflux disease.[85] *This review was not designed to compare the efficacy of different proton pump inhibitors.* The primary efficacy outcome of the review was heartburn remission, defined as mild heartburn on no more than 1 day per week. Proton pump inhibitors were superior to placebo for heartburn remission and overall symptom improvement. Proton pump inhibitors also were more effective than H2 receptor antagonists for heartburn remission in empirically treated patients (pooled relative risk 0.69; 95% CI 0.61 to 0.77), but not in patients with nonerosive gastroesophageal reflux disease (pooled relative risk 0.74; 95% CI 0.53 to 1.03). However, only 3 trials compared proton pump inhibitors with H2 receptor antagonists in nonerosive gastroesophageal reflux disease.

Another systematic review evaluated the efficacy of proton pump inhibitors for resolution of heartburn in patients with nonerosive gastroesophageal reflux disease.[86] This review searched literature through 2002, including the US Food and Drug Administration website. 7 placebo-controlled trials (3 published and 4 unpublished) were included: 2 rabeprazole, 2 esomeprazole, and 3 omeprazole. In patients with nonerosive gastroesophageal reflux disease, the risk difference in comparisons with placebo for resolution of heartburn at 4 weeks was 25% (95% CI 18 to 31). The review does not provide evidence about comparative efficacy of different proton pump inhibitors in patients with nonerosive gastroesophageal reflux disease.

Table 10 shows rates of heartburn remission rates and complete symptom relief calculated from data provided in the Cochrane review.[85] Similar proportions of patients experienced heartburn resolution or complete symptom relief across the drugs.

Table 10. Percent patients with resolution of heartburn at 4 weeks from Cochrane review[40]

	Endoscopically verified nonerosive gastroesophageal reflux disease		Presumptive treatment of symptoms	
Drug, dose	Number of trials	%, range	Number of trials	%, range
Esomeprazole 20 mg	2	61% to 62%		
Esomeprazole 40 mg	2	57% to 71%		
Esomeprazole 40 mg			1	84%
Omeprazole 10 mg or 20 mg			1	75%
Omeprazole 10 mg or 20 mg	4	56% to 95%		
Omeprazole 20 mg	5	58% to 84%	4	60% to 70%
Omeprazole 40 mg	1	95%		
Pantoprazole 20 mg			1	81%
Pantoprazole 40 mg	1	57%	1	66%
Rabeprazole 10 mg or 20 mg	1	98%		

We identified 1 additional placebo-controlled[87] and 1 active-control (ranitidine) trial[88] published since this review (Evidence Table 3). In a fair-quality trial of empiric treatment of patients with symptoms of gastroesophageal reflux disease, more patients taking pantoprazole 20 mg than ranitidine 300 mg were free of gastroesophageal reflux disease symptoms (heartburn, acid eructation, and pain on swallowing) at 4 weeks (68% compared with 43%).[88] In a fair- to poor-quality, 8-week, placebo-controlled trial of patients with endoscopically verified nonerosive gastroesophageal reflux disease whose primary symptom was upper abdominal discomfort, patients taking lansoprazole 15 mg had fewer days with upper abdominal discomfort and reduced severity of average daily pain.[87] Patients whose predominant symptom was heartburn were not included. It is not clear what proportion of patients was analyzed; patients were excluded from analysis for a specific endpoint if there were no data available for that endpoint.

Prevention of relapse

We identified only 1 head-to-head trial of maintenance treatment in patients with nonerosive gastroesophageal reflux disease.[89] We also included 2 placebo-controlled trials of on-demand rabeprazole[90] and esomeprazole[91] and a placebo-controlled trial of scheduled of omeprazole.[92] Details of these trials are shown in Evidence Table 5. Three other trials included patients with endoscopically verified nonerosive and erosive gastroesophageal reflux disease, but did not report results separately by group.[40, 93, 94]

A head-to-head trial compared on-demand esomeprazole 20 mg with scheduled lansoprazole 15 mg for 6 months in patients with endoscopically verified nonerosive gastroesophageal reflux disease who had experienced complete relief of heartburn with esomeprazole 20 mg during an acute treatment phase (2 to 4 weeks).[89] Patients were not blinded to treatment and the primary outcome measure was time to discontinuation from the maintenance phase due to unwillingness to continue. Patients also recorded heartburn and other symptoms on diary cards and were asked about their satisfaction with treatment during scheduled clinic visits.

By 6 months, significantly more patients receiving lansoprazole 15 mg were unwilling to continue than patients receiving esomeprazole 20 mg on demand (13% compared with 6%, $P=0.001$). More patients in the lansoprazole group said they discontinued because of adverse events (7.4% compared with 2.3%, $P=0.0028$), but discontinuations because of heartburn were not significantly different between treatment groups (4.8% for lansoprazole and 2.9% for esomeprazole, *P* value reported as NS). At 1 month, more esomeprazole patients were satisfied with their treatment, but at 3 and 6 months there was no difference between treatment groups on this measure. During the maintenance phase, the mean frequency of heartburn symptoms was higher in the on-demand esomeprazole group than the scheduled lansoprazole group.

Two 6-month placebo-controlled studies reported efficacy of on-demand therapy with rabeprazole 10 mg[90] or esomeprazole 20 mg[91] in patients with endoscopically verified nonerosive gastroesophageal reflux disease. In both studies, only patients who experienced complete symptom relief during an acute treatment phase were enrolled in the maintenance phase. In the study of rabeprazole 10 mg, rate of discontinuation due to inadequate heartburn control was 20% for placebo and 6% for rabeprazole ($P<0.00001$). Although mean length of heartburn-free periods was similar between groups, the time required for resolution of an episode of heartburn was significantly shorter with rabeprazole than placebo. In the study of esomeprazole 20 mg, 14% of patients taking esomeprazole discontinued the study drug compared with 51% taking placebo. Discontinuation was mainly due to inadequate control of heartburn ($P<0.0001$).[91]

In a placebo-controlled trial of daily omeprazole 10 mg, 27% of patients taking omeprazole discontinued the drug due to inadequate control of heartburn over 6 months compared with 52% of patients taking placebo.[92]

Children

There were no head-to-head trials of proton pump inhibitors in children. Placebo-controlled and active-control trials in children are shown in Evidence Table 6.

A fair-quality placebo-controlled trial of omeprazole (10 to 20 mg daily) in infants (3 to 12 months old) with gastroesophageal reflux defined as a gastric pH <4 for 5% of the monitoring time (unspecified) and/or abnormal esophageal histology found no difference in the cry/fuss time or visual analog scale scores of parent-assessed irritability between placebo and omeprazole.[95] Histologic and pH measures improved significantly with omeprazole but not placebo.

A poor-quality trial comparing omeprazole (40 mg daily per 1.73 square meters body surface area) with high-dose ranitidine (20 mg/kg daily) in children with reflux refractory to standard-dose ranitidine found both drugs to be effective; but, high dropout rate (19%), lack of intention-to-treat analysis, and inadequate reporting of baseline characteristics make these results unreliable.[96]

Key Question 2. What is the comparative effectiveness of different proton pump inhibitors in treating patients with peptic ulcer and nonsteroidal anti-inflammatory drug-induced ulcer?

Summary

Duodenal ulcer

- The data on comparative effectiveness of various proton pump inhibitors for treating duodenal ulcer were strong, with 10 head-to-head trials. Omeprazole 20 mg daily was typically the comparison.
- The evidence was strong for omeprazole and lansoprazole having similar effectiveness in both symptom relief and endoscopically verified healing. The pooled risk difference for 5 trials comparing daily lansoprazole 30 mg with omeprazole 20 mg was –0.2 (95% CI –3.0 to +2.6).
- The evidence for pantoprazole, rabeprazole, and esomeprazole was less strong because there are only single studies for each newer drug compared with omeprazole and no comparisons to other proton pump inhibitors.
- No evidence of a difference in healing rate among proton pump inhibitors.
- Symptom relief was an important measure in ulcer disease and did not always correlate with healing confirmed by endoscopy. Method of assessing symptom relief varied across studies and reporting of findings was often limited to early time points and few outcome measures (of many measured). Few studies found a difference in any of the many measures of symptom relief and the lack of reported data from later time points may indicate that symptom relief at those time points was equivalent for different proton pump inhibitors.

Gastric ulcer

- Comparative data about proton pump inhibitors for the treatment of gastric ulcer was very limited, with 3 studies comparing rabeprazole with omeprazole. No significant difference in healing rates was found.
- Symptom relief was better with rabeprazole 20 mg than omeprazole 20 mg in 3 of 12 measures at 3 weeks and in 2 measures at 6 weeks but no difference in symptom relief was found between rabeprazole 10 mg and omeprazole 20 mg daily.

Nonsteroidal anti-inflammatory drug-induced ulcer

- There were no head-to-head trials.
- Only 4 trials compared a proton pump inhibitor with another drug: 2 with omeprazole, 1 with esomeprazole, and 1 with lansoprazole. No differences between proton pump inhibitors could be discerned from these studies; confidence intervals for healing rates overlapped.

Detailed Assessment

Direct evidence

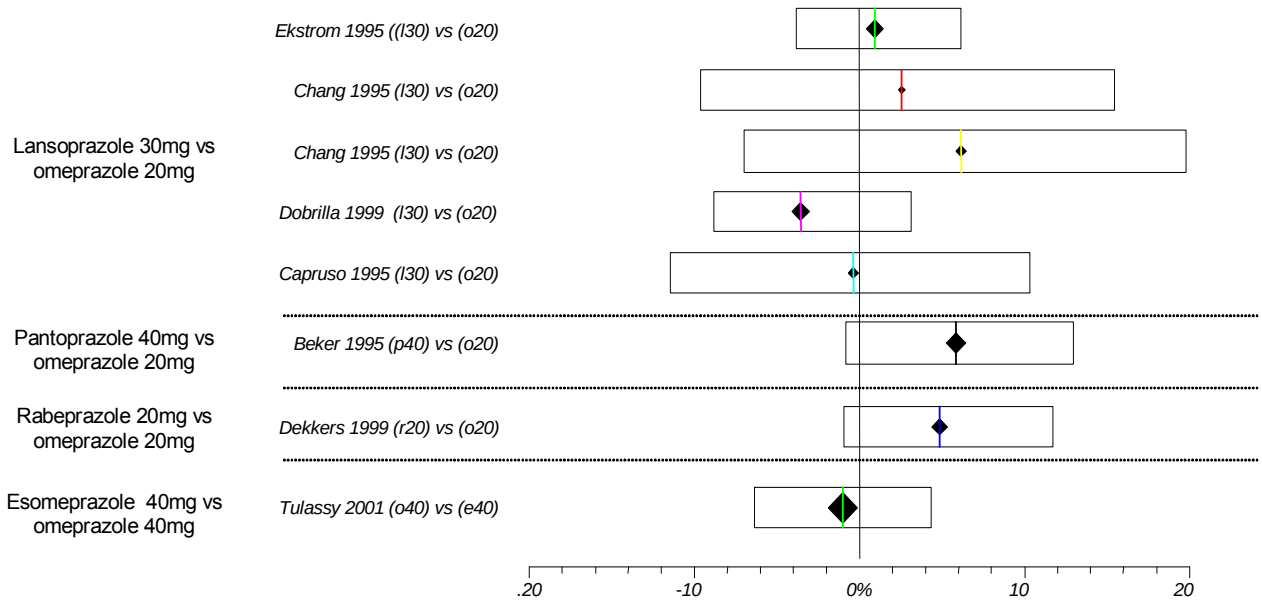
Duodenal ulcer

Ten randomized controlled trials compared one proton pump inhibitor with an equipotent dose of another.[41, 97-105] The details of these studies are summarized in Evidence Table 7. Six of these trials compared lansoprazole 30 mg with omeprazole 20 mg.[97-101, 104] One study each compared pantoprazole 40 mg and rabeprazole 20 mg with omeprazole 20 mg,[41, 102] 1 study compared esomeprazole 40 mg with omeprazole 40 mg daily (20 mg twice daily for each),[103] and 1 small study compared omeprazole enteric coated capsules with omeprazole magnesium.[105]

The studies were fair quality. They were generally similar with respect to design and demographics, with the following exceptions: One study was unusual in that as a part of an *Helicobacter pylori* eradication regimen, patients with active duodenal ulcer were given esomeprazole plus antibiotics for only 1 week while omeprazole patients received antibiotics plus omeprazole for 1 week then continued omeprazole (only) for another 3 weeks.[103]

As shown in Figure 8, omeprazole 20 mg, lansoprazole 30 mg, rabeprazole 20 mg, and pantoprazole 40 mg did not differ in the percentage of patients with duodenal ulcer that was healed by 4 weeks compared with omeprazole 20 mg daily. The pooled risk difference for daily lansoprazole 30 mg compared with omeprazole 20 mg was –0.2 (95% CI –3.0 to +2.6). The risk differences found between esomeprazole 40 mg, pantoprazole 40 mg, and rabeprazole 20 mg and omeprazole were approximately –0.97%, 6%, and 5%, respectively; however, these estimates were based on single studies and were not statistically significant. Similarly, no difference in healing rate was found between omeprazole enteric coated capsules and omeprazole magnesium both at 40 mg daily with all 57 patients being healed at 4 weeks.[105] Results from a large multicenter trial comparing esomeprazole 20 mg twice daily with omeprazole 20 mg twice daily also showed no difference in healing rate.[103] The results for healing at 2 weeks were similar for all comparisons.

Figure 8. Duodenal ulcer healing at 4 weeks in trials comparing proton pump inhibitors



(Note: size of diamond corresponds to study sample size)

Study	Percent risk difference (95% CI)
Lansoprazole 30 mg vs. omeprazole 20 mg once daily	
Ekstrom 1995	0.96 (–3.80 to 6.15)
Chang 1995	2.55 (–9.62 to 15.5)
Chang 1995	6.14 (–7.0 to 20)
Dobrilla 1999	–3.57 (–8.84 to 3.14)
Capruso 1995	–0.34 (–11.41 to 10.32)
	Pooled risk difference = –0.2 (–3.0 to 2.6)
Pantoprazole 40 mg vs. omeprazole 20 mg once daily	
Beker 1995	5.85 (–0.84 to 12.95)
Rabeprazole 20 mg vs. omeprazole 20 mg once daily	
Dekkers 1999	4.84 (–0.96 to 11.70)
Esomeprazole 40 mg vs. omeprazole 40 mg once daily	
Tullassay 2001	–0.97 (–6.4 to 4.35)
Omeprazole enteric-coated capsule 40 mg vs. omeprazole magnesium 40 mg once daily	
Liang 2008	0 (100% healed in both groups)

Symptoms (pain, nausea, vomiting, antacid use, and overall well-being) were assessed by investigators at visits and through patient diaries in 8 studies. Only 1 study found a significant difference between proton pump inhibitors.[41] Daytime pain was "improved" in 92% of the rabeprazole group and 83% of the omeprazole group at 4 weeks (P=0.038), however, no difference was found in nighttime pain or in the number of patients without pain. Antacid use, gastrointestinal symptoms, and overall well-being were not different in any of the studies.

Only 1 head-to-head study addressed maintenance, comparing lansoprazole 15 mg, lansoprazole 30 mg, and omeprazole 20 mg for up to 12 months (see Evidence Table 8).[100] At 6 months after healing, recurrence rates were 4.5%, 0%, and 6.3%, respectively. At 12 months the recurrence rates were 3.3%, 0%, and 3.5%, respectively. These differences were not statistically significant.

Gastric ulcer

Four studies directly compared proton pump inhibitors in treating gastric ulcer.[106-109] Three fair-quality trials compared rabeprazole 10 or 20 mg to omeprazole 20 mg daily.[106, 108, 109] Early healing was measured at 1 to 3 weeks and final healing was measured at 6 or 8 weeks. All 3 trials found no difference in endoscopically verified healing at 6 or 8 weeks. A fair-quality study of 227 patients compared rabeprazole 20 mg with omeprazole 20 mg (Evidence Table 9).[106] The percent risk difference in the rate of healing at 3 weeks was –3% (95% CI –16 to +9.7) and was reported as the same at 6 weeks. Twelve different comparisons of symptom resolution or improvement were made. No significant differences were found in pain resolution or improvement (frequency, severity, night, or daytime) at 3 or 6 weeks for 9 of these comparisons. Rabeprazole was statistically superior in 3 comparisons: improvement of severity of pain at 3 weeks, improvement in the frequency of daytime pain at 3 weeks, and resolution of nighttime pain at 6 weeks. No difference in change in overall well-being or in antacid use was found.

The 2 small fair quality trials comparing the lower dose of rabeprazole (10 mg) also found no difference, with a pooled relative risk of 1.0 (95% CI 0.9 to 1.2) using a random effects model and intention to treat analysis (assuming missing values to be unhealed).[108, 109] In 1 of these trials symptom resolution was also found to be similar between groups at 6 weeks (64% each; P=0.958).[109] Analysis of patient CYP2C19 genotype in both studies did not indicate a difference in healing rate at 6 or 8 weeks among those who were categorized as extensive or poor metabolizers. However, the 2 studies found different results for the ulcer size reduction at early time points. The first study (80 patients) found rabeprazole to result in similar reductions in ulcer size at 2 weeks regardless of CYP2C19 genotype but omeprazole resulted in smaller improvements among those who were categorized as homozygous extensive metabolizers.[108] The second study (112 patients) found no differences.[109]

A poor-quality trial compared lansoprazole 30 mg daily with omeprazole 20 mg daily.[107] This study did not conduct an intent-to-treat analysis and more patients in the omeprazole group (15%) were excluded from analysis than the lansoprazole group (7%). Although the authors state there were no differences between groups at baseline, 4% of patients in the omeprazole group were smokers, compared with 1% in the lansoprazole group. The results of this study found lansoprazole superior in cumulative healing rate at 8 weeks (93% compared with 82%, P=0.04); the difference at 4 weeks was not statistically significant. It is not clear from the publication which patients were included in this analysis and our statistical analyses based on differing assumptions did not result in statistically significant differences between the groups at either time point. Differences in symptom relief were not statistically significant.

Treatment of nonsteroidal anti-inflammatory drug-induced ulcer

No study compared one proton pump inhibitor with another.

Indirect evidence

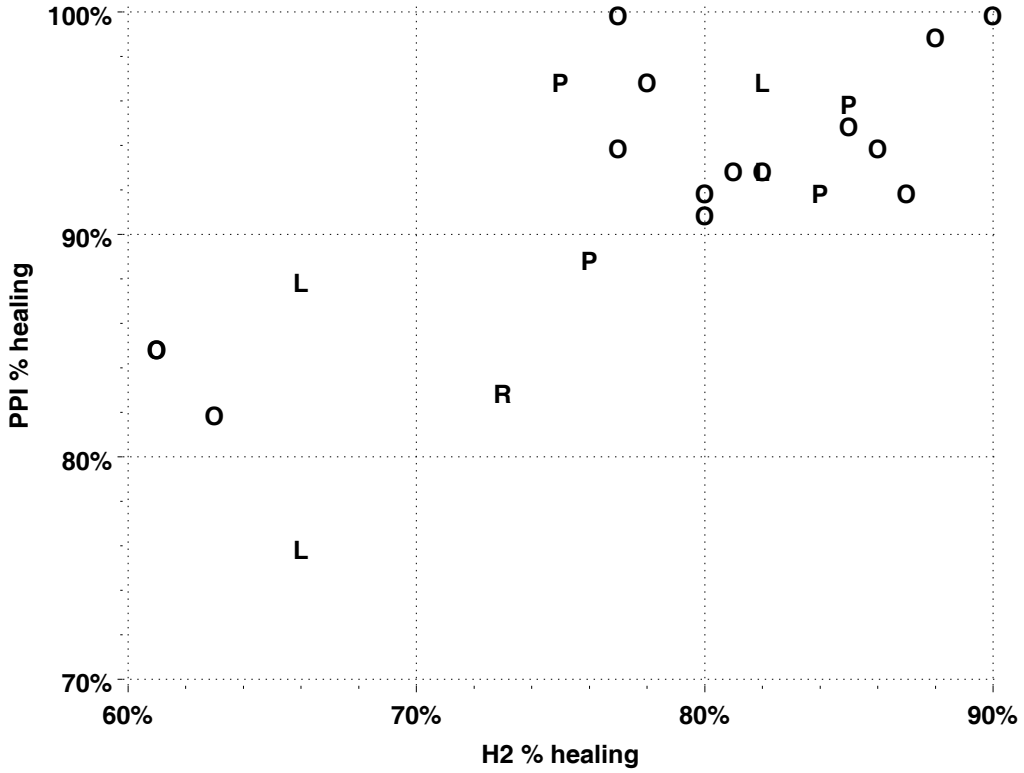
Duodenal ulcer

Twenty-five randomized controlled trials compared a proton pump inhibitor with an H2 receptor antagonist. Of these, 22 papers were reviewed.[110-135] Since these studies could only be used to make indirect comparisons of the effectiveness of the various proton pump inhibitors, we presented a limited analysis. The most common H2 receptor antagonist used in comparisons was ranitidine 300 mg daily, with 10 studies comparing omeprazole 20 mg. There were no studies comparing esomeprazole with an H2 receptor antagonist.

Figure 9 shows rates of healing at 4 weeks in 21 studies comparing a proton pump inhibitor with an H2 receptor antagonist for treatment of duodenal ulcer. Proton pump inhibitors were more effective than H2 receptor antagonists, but there was no significant difference in healing rate among the proton pump inhibitors. With omeprazole and lansoprazole, healing rate was correlated with H2 receptor antagonists' healing. That is, as the healing rate in the H2 receptor antagonist group increased, proton pump inhibitor healing rate increased. One comparison showed pantoprazole to have a significantly higher healing rate than rabeprazole (risk difference 11.3%), but this comparison was made in only 1 study, and the confidence interval is large (95% CI 2.4 to 23.2).

Another study[132] examined the added benefit of continuing omeprazole 20 mg for 3 additional weeks after 1 week of eradication therapy with omeprazole 20 mg plus amoxicillin 1000 mg and clarithromycin 500 mg. At 4 weeks, there was no difference in healing rates in patients assigned to omeprazole (89%) and placebo (87%). Another reported symptom relief only.[131]

Figure 9. Duodenal ulcer healing at 4 weeks in comparisons of proton pump inhibitor with H2 receptor antagonist



Duodenal ulcer healing rate at 4 weeks

Estimated healing rate	When H2 healing is…	Mean	95% CrI	
Lansoprazole	60%	73.3%	55.8%	86.9%
	73%	89.6%	85.0%	93.5%
	80%	93.9%	89.5%	97.1%
	90%	97.0%	92.6%	99.3%
Omeprazole	60%	82.6%	75.5%	88.7%
	73%	90.9%	88.7%	93.1%
	80%	93.7%	91.9%	95.4%
	90%	96.3%	94.5%	97.8%
Pantoprazole	—	93.9%	90.9%	96.2%
Rabeprazole	—	82.6%	70.9%	91.1%
Difference between proton pump inhibitors	**When H2 healing is…**	**Mean difference**	**95% CrI**	
Lansoprazole vs. omeprazole	60%	–9.3%	–28.1%	6.1%
	80%	0.2%	–4.6%	3.8%
	90%	0.8%	–4.0%	3.8%
Lansoprazole vs. pantoprazole	80%	0.0%	–5.0%	4.4%
Lansoprazole vs. rabeprazole	73%	7.0%	–2.5%	19.3%
Omeprazole vs. pantoprazole	80%	–0.2%	–3.1%	3.3%
Omeprazole vs. rabeprazole	73%	8.3%	–0.2%	20.3%
Pantoprazole vs. rabeprazole	—	11.3%	2.4%	23.2%

Gastric ulcer

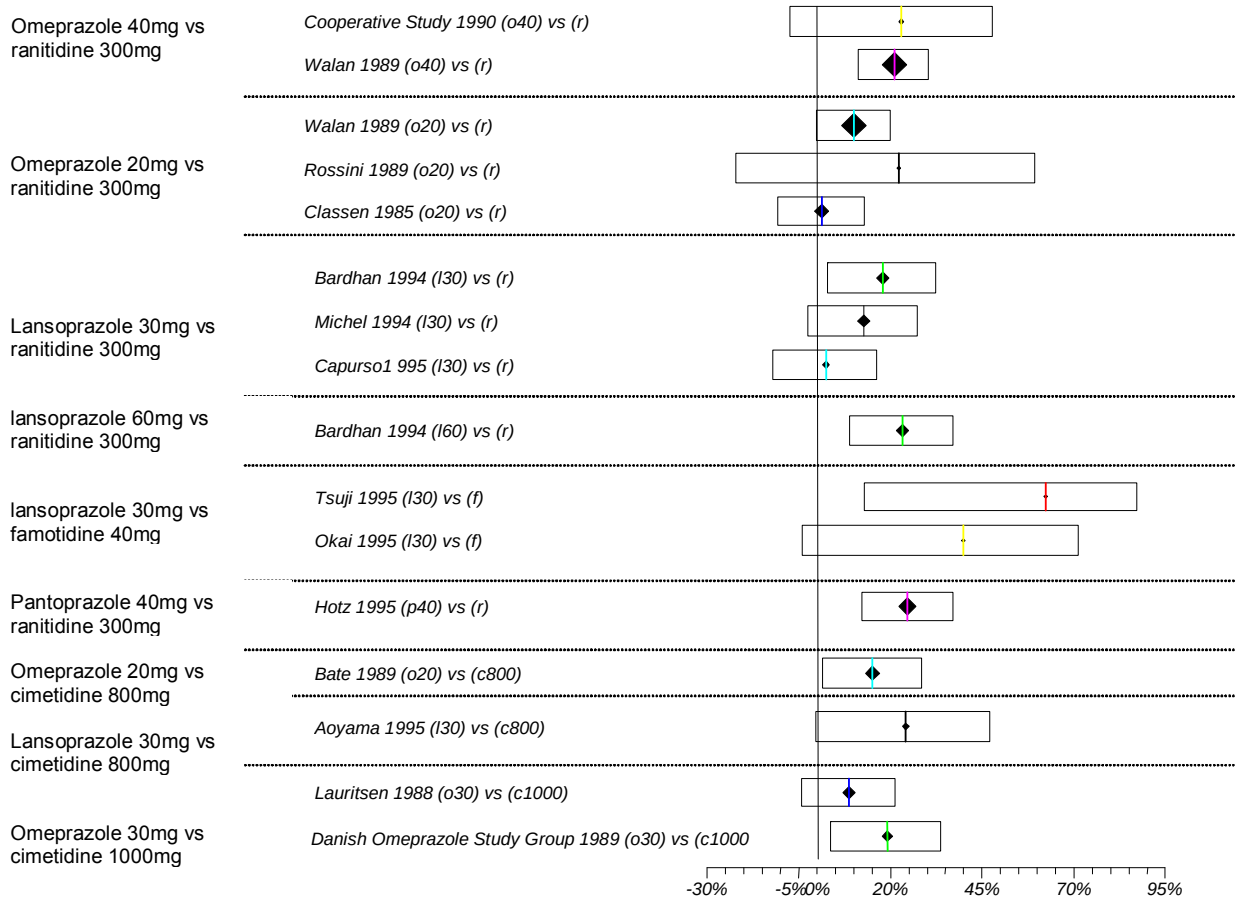
Fifteen studies compared a proton pump inhibitor with an H2 receptor antagonist for treatment of gastric ulcer (Evidence Table 9).[101, 110, 136-148] Two looked at maintenance therapy[149-151] and 1 was a follow-up of healed patients from another study.[98] One of the maintenance studies included patients with either gastric or duodenal ulcer, all of which were resistant to H2 receptor antagonist therapy.[151] The other evaluated healing of gastric ulcer with esomeprazole compared with ranitidine in patients who continued to take a nonsteroidal anti-inflammatory drug.[136] This study is examined under Key Question 3. No study compared rabeprazole with a H2 receptor antagonist. Of the 15 trials, 5 compared omeprazole with ranitidine; 3 compared lansoprazole with ranitidine; 1 compared pantoprazole with ranitidine; 2 compared lansoprazole with famotidine; 3 compared omeprazole with cimetidine, and 1compared lansoprazole with cimetidine.

The total follow-up times varied, but healing rates at 4 weeks were available from all studies. Differences in the percentages of patients healed with different proton pump inhibitors at 4 weeks are plotted in Figure 10. The pooled risk differences range from 1.1% to 62.5%, with the smallest studies showing larger effects. The confidence intervals of the risk differences for healing with proton pump inhibitors compared with H2 receptor antagonists all overlap.

Symptoms were assessed by investigators at visits and through patient diaries in 13 studies. One did not report symptoms.[139] Pain was the most commonly assessed symptom. The pain scales differed among studies (0 to 3 in some, 0 to 4 in others) and sometimes were not described. Most studies found that the proton pump inhibitor relieved symptoms somewhat more quickly, with no difference later on between groups in percentage of patients without pain. However, only 3 studies found statistically significant differences on symptom measures, and then only in some of the many measures assessed.

One study[152] reported maintenance therapy for the comparison of lansoprazole 15 mg or 30 mg with placebo. Lansoprazole was effective for preventing endoscopically verified recurrence, eliminating symptoms, and reducing antacid use. A 6-month open study reported that omeprazole 20 mg daily as more effective than ranitidine in preventing relapse in patients with refractory ulcer (unhealed after 8 weeks of treatment with an H2 receptor antagonist).[151] In this study only 12 patients of 102 enrolled were assigned to ranitidine, and patients with either gastric or duodenal ulcer were included. A 6-month follow-up study without treatment[149] looked at patients who had healed with 6 weeks of treatment with omeprazole or cimetidine;[138] no significant difference was found in relapse rate. All of these studies had high or differential dropout rates.

Figure 10. Gastric ulcer healing at 4 weeks in comparisons of proton pump inhibitor with H2 receptor antagonist



(Note: size of diamond corresponds to study sample size)

Study	Percent risk difference (95% CI)
Cooperative Study 1990 (o40) vs. (r)	22.92 (–7.50 to 47.83)
Walan 1989 (o40) vs. (r)	21.02 (11.31 to 30.37)
Walan 1989 (o20) vs. (r)	9.97 (–0.19 to 19.92)
Rossini 1989 (o20) vs. (r)	22.22 (–22.28 to 59.36)
Classen 1985 (o20) vs. (r)	1.09 (–10.66 to 12.83)
Bardhan 1994 (l30) vs. (r)	17.82 (2.82 to 32.26)
Michel 1994 (l30) vs. (r)	12.66 (–2.53 to 27.31)
Capurso1 995 (l30) vs. (r)	2.43 (–12.18 to 16.35)
Bardhan 1994 (l60) vs. (r)	23.22 (8.78 to 37.08)
Tsuji 1995 (l30) vs. (f)	62.50 (12.85 to 87.18)
Okai 1995 (l30) vs. (f)	40.00 (–4.08 to 71.22)
Hotz 1995 (p40) vs. (r)	24.67 (12.15 to 37.01)
Bate 1989 (o20) vs. (c800)	15.08 (1.45 to 28.38)
Aoyama 1995 (l30) vs. (c800)	24.06 (–0.38 to 47.17)
Lauritsen 1988 (o30) vs. (c1000)	8.56 (–4.24 to 21.27)
Danish Omeprazole Study Group 1989 (o30) vs. (c1000 mg)	19.07 (3.49 to 33.82)

Treatment of nonsteroidal anti-inflammatory drug-induced ulcer

Four studies compared proton pump inhibitors (omeprazole, esomeprazole, and lansoprazole) with another drug in healing ulcers induced by nonsteroidal anti-inflammatory drugs.[136, 153-155] The details of these studies are summarized in Evidence Table 10. A good-quality systematic review of prevention and treatment of nonsteroidal anti-inflammatory drug-induced ulcers was also found.[156]

Comparisons of ranitidine 150 mg twice daily with omeprazole 20 and 40 mg daily, lansoprazole 15 and 30 mg daily, and esomeprazole 20 and 40 mg once daily showed higher rates of healed ulcer at 8 weeks for the proton pump inhibitors.[136, 153, 155] The risk difference in percent healed ranged from 14% to 22% favoring the proton pump inhibitor; in all comparisons the difference was statistically significant. While there is no direct comparison of the proton pump inhibitors, all confidence intervals overlap, suggesting it is unlikely that a difference would be found. Direct comparisons would be needed to confirm this suggestion. A single study found that omeprazole 20 mg was superior to misoprostol in healing rate at 8 weeks, but 40 mg was not superior.[154]

One study[154, 157] assessed quality of life using the Gastrointestinal Symptom Rating Scale and the Nottingham Health Profile. On the Gastrointestinal Symptom Rating Scale, omeprazole was better than misoprostol in the change in score on the total scale and on the reflux and diarrhea subscales. Although the improvement in score was greater with 20 mg omeprazole than 40 mg, the differences were not statistically significant. Only the sleep score of the Nottingham Health Profile was reported, which also showed omeprazole 20 mg to be superior to misoprostol, but the change in score for omeprazole 40 mg was not reported.

Key Question 3. What is the comparative effectiveness of different proton pump inhibitors in preventing ulcer in patients taking a nonsteroidal anti-inflammatory drug?

Summary

- Direct comparison of pantoprazole 20 mg, 40 mg, and omeprazole 20 mg daily did not indicate statistically significant differences in rates of therapeutic or endoscopic failure at 6 months in a group of patients taking nonsteroidal anti-inflammatory drugs regularly for arthritic conditions.
- A good-quality systematic review and 7 subsequently published trials compared proton pump inhibitors with placebo or other drugs. Only 1 trial included outcome measures for serious complications; for some of the endoscopic findings, patients were asymptomatic.
- For development of symptoms, new ulcers, or serious erosions, the studied proton pump inhibitors (omeprazole, lansoprazole, and pantoprazole) showed no difference. However, confidence in this finding is low because of differences in patient populations, comparison groups, and outcome measures.

Detailed Assessment

Direct evidence

In a study of 595 patients with arthritic diseases, continuously taking an nonsteroidal anti-inflammatory drug (not including COX-2 Inhibitors), and considered at high risk for

gastrointestinal injury (previous ulcer or taking anticoagulants), patients were randomized to 6 months of pantoprazole 20 mg or 40 mg or omeprazole 20 mg daily.[158] Using life-table analysis methods, remission rates were compared across and between groups. The primary outcome, therapeutic failure, was defined as peptic ulcer, >10 erosions, reflux esophagitis, and discontinuations of study drug due to an adverse event or severe gastrointestinal symptoms. Examination of baseline risk characteristics revealed that the pantoprazole 40 mg group had fewer patients taking anticoagulants (1% compared with 4%), experiencing a change in nonsteroidal anti-inflammatory drug in the last month (6% compared with 9% or 10%), and fewer with a history of endoscopically proven peptic ulcer (20% compared with 24% or 25%). These differences are small but may have biased the risk level in favor of the pantoprazole 40 mg group. Patients were censored from the analyses (considered lost to follow up) if they had low adherence to the nonsteroidal anti-inflammatory drug regimen, found to not meet inclusion after randomization, failed to adhere to the protocol, or withdrew from the study due to an adverse event not considered related to study drugs or due to "refusal to continue". The numbers of patients censored for these reasons were greater in the omeprazole group (N=42) and lowest in the pantoprazole 40 mg group (N=29). With these issues in mind, we rate this trial as fair quality (rather than poor quality, as it does meet other aspects of internal validity) and suggest caution in interpreting the results. There was no statistically significant difference between the groups in remission rates based on either therapeutic failure or failure limited to endoscopic findings, with more than 90% of patients remaining in remission in all groups at 3 and 6 months.

Indirect evidence

One good-quality systematic review addressed the question of proton pump inhibitors for treatment of nonsteroidal anti-inflammatory drug-induced ulcer.[159] Its search for literature covered 1966 to 2000 (MEDLINE search from 1966 to January 2000, Current Contents for 6 months prior to January 2000, EMBASE to February 1999, and a search of the Cochrane Controlled Trials Register from 1973 to 1999). The review found 5 randomized trials that assessed omeprazole 20 mg with 40 mg in prevention of nonsteroidal anti-inflammatory drug-induced gastroduodenal toxicity. None of the studies were designed to evaluate the effectiveness of proton pump inhibitors in preventing serious complications of ulcers (hemorrhage, perforation, or death). The review showed that omeprazole is superior to the H2 receptor antagonists but provided no data on any other proton pump inhibitor.

Eight trials published more recently[154, 155, 160-165] than the omeprazole review are presented in Evidence Table 11. None of these studies was a head-to-head comparison and there were important differences in treatment regimens and follow-up, making comparisons across studies impossible. All the trials enrolled patients who were regular users of nonsteroidal anti-inflammatory drugs, with 1 including COX-2 Inhibitors.[165] Symptom assessment and reporting varied among these studies.

One study[160] included only patients *without Helicobacter pylori* who were randomized to received placebo, misoprostol 800 µg, lansoprazole 15 mg, or 30 mg with follow-up at 1, 2, and 3 months, while another study[162] included patients with *Helicobacter pylori* who developed ulcer complications (bleeding, perforation, or obstruction) after a month of daily low-dose aspirin. After ulcers were healed and *Helicobacter pylori* were eradicated, patients continued with aspirin 100 mg and were randomized to lansoprazole 30 mg or placebo. In the last study of *Helicobacter pylori* and prevention of nonsteroidal anti-inflammatory drug-induced ulcers,[163] patients with *Helicobacter pylori* but without past or current ulcer were assigned to 1 of 4 treatment groups:

omeprazole 20 mg plus clarithromycin 500 mg and amoxicillin 1 gram for 1 week; placebo or omeprazole 20 mg daily for 4 weeks; omeprazole 20 mg once daily for 5 weeks; or placebo for 5 weeks.

In the study of *Helicobacter pylori* negative patients,[160] lansoprazole was inferior to misoprostol in preventing gastric ulcers. At 3 months, the gastric ulcer rate (failure rate) was 7% for misoprostol, 20% for lansoprazole 15 mg, and 18% for lansoprazole 30 mg, with no significant difference between lansoprazole doses. However, when adverse effects were included as failures, the failure rate for all 3 treatment groups was 31%. A post hoc subgroup analysis of patients taking nonsteroidal anti-inflammatory drugs and low dose aspirin found no significant difference among treatments at 12 weeks.[166] Symptoms (antacid use and day and nighttime abdominal pain) were assessed by patient diary and were found to be significantly better in the lansoprazole groups than the misoprostol group, but comparisons between the 2 lansoprazole doses were not made.[160]

In the study of *Helicobacter pylori* positive patients with ulcer complications (bleeding, perforation, or obstruction),[162] the primary endpoint was prevention of ulcer complications and the secondary endpoint was recurrence. The rate of recurrence of ulcer complications at a median follow-up of 12 months was 1.6% in the lansoprazole group compared with 14.8% in the placebo group. Two patients in the placebo group (N=61) were also taking nonsteroidal anti-inflammatory drugs.

In patients with *Helicobacter pylori* but no history of ulcer, all 3 active treatment regimens were better than placebo in reducing the occurrence of ulcer and dyspeptic symptoms requiring therapy. There were no significant differences between the treatment groups.

A study comparing pantoprazole with placebo[161] presented a life-table analysis rather than simple proportions of patients without ulcer, making comparison with other placebo-controlled studies of proton pump inhibitors difficult. The pantoprazole group had 17% fewer ulcers at 4 weeks and 27% at 12 weeks. Patients who dropped out due to adverse events were included in the 4 week data as treatment failures. The methods or scales used to assess symptoms were not described but reported just "symptoms."[161] Presence of gastrointestinal symptoms differed at baseline in the 2 groups: They were present in 43% of the pantoprazole group and 18% of the placebo group. At 4 and 12 weeks presence of gastrointestinal symptoms improved in the pantoprazole group (to 17% and 20%, respectively), while in the placebo group remained stable (20% and 19%, respectively).

The only evidence on prevention of ulcers related to COX-2 inhibitors came from a combined report of 2 similar fair quality trials that enrolled patients who were regularly taking a nonselective nonsteroidal anti-inflammatory drug or a COX-2 inhibitor and were at risk of peptic ulcer (age > 60 years or documented peptic ulcer in last 5 years).[165] Combined, the studies randomized 1429 patients to esomeprazole 20 mg, esomeprazole 40 mg, or placebo daily for 6 months. Using pooled and separate life-table analyses, the overall analysis indicated that both esomeprazole groups prevented peptic ulcer statistically significantly more often than placebo for all nonsteroidal anti-inflammatory drugs. While no statistical analyses were undertaken comparing the 2 doses of esomeprazole, the rates of ulcer development were very similar (5.2% with 20 mg and 4.6% with 40 mg). The rates of ulcer development among the subgroup taking a COX-2 inhibitor were also statistically significantly lower with either dose of esomeprazole compared to placebo (16.5% with placebo compared with 0.9% and 4.1% with 20 mg and 40 mg of esomeprazole, respectively). The separate study analyses of the subgroup taking nonselective nonsteroidal anti-inflammatory drugs indicated that esomeprazole was superior to placebo in one

trial (N=844) but not in the other (N=585), while the pooled analysis indicated statistically significant benefit with either dose of esomeprazole compared to placebo.

Key Question 4. What is the comparative effectiveness of different proton pump inhibitors in eradicating *Helicobacter pylori* infection?

Summary

- The evidence on comparative effectiveness of various proton pump inhibitors was fair, despite 5 systematic reviews and 29 head-to-head trials. The significant heterogeneity in design, participants, and method of measuring outcomes among studies lessen the strength of the evidence.
- Pooled analysis of eradication rates stratified by number of days of treatment and dose comparison did not find statistically significant differences in eradication rate among the proton pump inhibitors.
- In children evidence was extremely limited, with only 2 trials, both of which compared lansoprazole with placebo. Neither trial found the addition of lansoprazole to result in higher eradication rates than antibiotic therapy alone.

Detailed Assessment

Direct evidence

Five systematic reviews have evaluated the efficacy of proton pump inhibitors in eradication of *Helicobacter pylori,* however because these reviews focused on comparisons to H2 receptor antagonists, were out of date (literature searches conducted prior to 2001), or included non-randomized studies or studies published only as abstracts, they were not sufficient to evaluate this question.[47, 167-171]

Twenty-nine studies directly compared one proton pump inhibitor with another, in combination with the same antibiotic(s), and reported *Helicobacter pylori* eradication rates.[98, 104, 172-198] They were fair-quality with the exception of 5 poor-quality studies that were not blinded or provided inadequate data to compare eradication rates directly.[183, 187, 192, 197, 199] Several studies included antibiotic regimens that are no longer standard.[187, 104, 178, 183, 190, 198, 200]

Of these, 23 trials compared proton pump inhibitors using identical regimens of antibiotics (within study) and reported eradication rates in a way that allowed statistical pooling (Table 11).[68, 104, 173, 175-180, 183-187, 189-191, 193-197, 201] All of these trials included treatment with 2 antibiotics and assessed *Helicobacter pylori* eradication at 4 to 6 weeks after treatment. While most of these trials used a 7 day proton pump inhibitor regimen in combination with 2 antibiotics, 3 trials used longer proton pump inhibitor regimens, a 14 day[190, 202] and a 30 day regimen.[175] Interestingly, these regimens resulted in lower eradication rates at follow-up. Overall, eradication rates ranged from 67% in a trial of lansoprazole 60 mg daily for 30 days to 100% in a trial of pantoprazole 40 mg daily for 7 days. Pooled rates of eradication from these trials vary (see Table 11 below), but pooled relative risks of these rates did not identify statistically significant differences between groups when stratified by number of days of treatment and dose comparison (Table 11 below). Several trials examined different dose levels (high compared to usual and low compared to usual) of proton pump inhibitors without finding statistically significant differences in eradication rates.

In 1 additional study, patients who had failed a 1 week regimen of amoxicillin, clarithromycin, and a proton pump inhibitor were randomized to rabeprazole 20 mg, lansoprazole 60 mg, or omeprazole 40 mg daily each plus amoxicillin and metronidazole.[188] No differences were found among the proton pump inhibitors in eradication rates, with 91% eradication in each group.

Table 11. Rates of eradication of *Helicobacter pylori*

Duration of proton pump inhibitor treatment Number of trials	Group A	Eradication rate (pooled)	Group B	Eradication rate (pooled)
Lansoprazole compared with omeprazole				
7 Days 4 trials	Lansoprazole 60 mg	83%	Omeprazole 40 mg	84%
14 Days 3 trials	Lansoprazole 60 mg	74%	Omeprazole 40 mg	77%
30 days 1 trial	Lansoprazole 60 mg	67%	Omeprazole 40 mg	76%
7 days 2 trials	Lansoprazole 30 mg	85%	Omeprazole 40 mg	84%
7 days 1 trial	Lansoprazole 30 mg	71%	Omeprazole 20 mg	78%
Pantoprazole compared with omeprazole				
7 days 2 trials	Pantoprazole 40 mg	85%	Omeprazole 40 mg	93%
7 days 3 trials	Pantoprazole 80 mg	78%	Omeprazole 40 mg	78%
Esomeprazole compared with omeprazole				
7 days 2 trials	Esomeprazole 40 mg	84%	Omeprazole 40 mg	79%
7 days 1 trial	Esomeprazole 80 mg	70%	Omeprazole 40 mg	65%
Rabeprazole compared with omeprazole				
7 days 1 trial	Rabeprazole 10 mg	71%	Omeprazole 20 mg	70%
7 days 2 trials	Rabeprazole 20 mg	72%	Omeprazole 40 mg	72%
7 -10 days 3 trials	Rabeprazole 40 mg	75%	Omeprazole 40 mg	72%
Rabeprazole compared with lansoprazole				
7 days 2 trials	Rabeprazole 20 mg	81%	Lansoprazole 60 mg	78%
7 days 2 trials	Rabeprazole 40 mg	89%	Lansoprazole 60 mg	84%
Rabeprazole compared with esomeprazole				
7 days 1 trial	Rabeprazole 40 mg	91%	Esomeprazole 40 mg	89%

Two systematic reviews addressed similar questions, 1 focusing on the comparison of esomeprazole to other proton pump inhibitors[203] and the other directly comparing proton pump inhibitors.[204] Both of these reviews were fair to poor quality because they pooled studies with differing proton pump inhibitor regimens (for example drug A given for 7 days compared to drug B given for 14 days) with those comparing similar regimens or provided inadequate details of studies included to determine the comparisons being made.

Indirect evidence in children

Two trials evaluated lansoprazole in eradication of *Helicobacter pylori* in children.[205, 206] Both studies used antibiotic regimens of amoxicillin and tinidazole, given for 6 or 7 days, in combination with lansoprazole or placebo. The 2 protocols were very similar, but not identical; in 1 the dose of lansoprazole was 30 mg daily with children 10 to 21 years eligible for enrollment,[205] while in the other dosing was based on weight (<20 kg, 15 mg daily; ≥20 kg, 30 mg daily)[206] and the age range was 8 to 14 years. However, the mean age for participants in both trials was 11 years. Neither trial resulted in significantly different eradication rates between placebo (58%[206] and 71%[205]) and lansoprazole (67%[206] and 68%[205]).

Key Question 5. Is there evidence that a particular treatment strategy is more effective or safer than another for longer-term treatment (more than 8 weeks) in patients with gastroesophageal reflux disease?

Summary

Standard dose compared with low-dose proton pump inhibitor

- Time in remission was longer for higher doses compared with lower doses for omeprazole and rabeprazole, but the same for higher and lower doses of lansoprazole. Evidence on esomeprazole was inconclusive.
- Rates of endoscopically verified remission at study end were greater with the higher dose of rabeprazole compared with the lower dose, but were not different between dose strategies for omeprazole and lansoprazole.
- Rates of relapse of symptoms were generally higher with lower doses of omeprazole, lansoprazole, and rabeprazole.

Standard dose compared with intermittent or on-demand proton pump inhibitor

- For patients with healed erosive esophagitis, a regimen of daily proton pump inhibitor was superior in preventing relapse of esophagitis or recurrence of symptoms compared with 3 days a week or on-demand regimens at 6 months.
- For patients with nonerosive esophagitis, assessments of symptom severity or relapse of symptoms was not different between daily and on-demand regimens. Patient satisfaction and quality of life ratings at study end were also not different, although the mean change in quality of life score from baseline was better with daily therapy.
- For patients presenting with symptoms of gastroesophageal reflux disease, but without endoscopic assessment, evidence is mixed.

Proton pump inhibitor compared with H2 receptor antagonist

- Daily proton pump inhibitor therapy was found superior to daily H2 antagonist therapy in preventing relapse of erosive esophagitis, or symptoms of gastroesophageal reflux disease.

Detailed Assessment

Standard-dose proton pump inhibitor compared with low-dose proton pump inhibitor

Eleven trials compared a standard dose of a proton pump inhibitor with a lower dose of the same proton pump inhibitor for longer-term treatment of gastroesophageal reflux disease (Evidence Table 13). Five trials compared lansoprazole 30 mg with lansoprazole 15 mg;[21, 207-210] 2 compared omeprazole 20 mg with omeprazole 10 mg;[211, 212]1 compared pantoprazole 40 mg with pantoprazole 20 mg;[213] 2 compared rabeprazole 20 mg with rabeprazole 10 mg; [214, 215] and 2 compared esomeprazole 40 mg with esomeprazole 20 mg and esomeprazole 10 mg.[216, 217] Eight trials also included a placebo arm. In most of the trials, the drug and dose used for acute treatment before maintenance treatment began was the same as the higher dose used in the maintenance phase. The studies' follow-up periods were 6 months in 4 trials, 12 months in 6 trials, and 5 years in 1 trial.[214] Of these, 2 were poor quality. One had significant differences in prognostic factors at baseline combined with other flaws relating to assignment of group.[209] In the other, patients with adverse events thought to possibly be or probably be related to the study drug were counted as having a relapse, the margin allowed for noninferiority was very large (20%), and there were flaws related to assignment of group.[213] These studies are not discussed below, and the remainder were fair quality.

All trials reported recurrence rate of endoscopically verified disease (either as relapse rates or remission rates) and the time in remission. Remission was considered grade 0 on any esophagitis scale in most studies, although some allowed grade 1 as well. All but 1 trial[212] also reported recurrence rate of symptoms or the number of patients with mild or no symptoms at study end. Study characteristics are summarized in Table 12 and results are shown in Table 13.

Time in remission

The duration of remission was statistically significantly greater with higher compared with lower doses of omeprazole at 6 months ($P<0.002$),[212] and rabeprazole at both 1 year ($P=0.016$) and 5 years ($P< 0.007$).[214, 215] Differences were not found between doses of lansoprazole in 3 studies.[21, 207, 208, 210] Additionally, 2 studies of esomeprazole and 1 of omeprazole did not make statistical comparisons between the doses.[211, 216, 217]

Endoscopically verified remission

Examining Table 13, the higher doses resulted in greater numbers of patients being relapse-free at 6 or 12 months but differences between the higher and lower proton pump inhibitor dose strategies were examined statistically in only 5 studies. All 3 studies of lansoprazole found no difference between the 15 mg daily and 30 mg daily doses at 12 months,[21, 207, 208] and a single trial found no difference in relapse rates between the standard dose of omeprazole (20 mg) compared with the lower dose (10 mg) at 12 months.[211] However, 1 study of rabeprazole found that patients taking the standard dose (20 mg) had a higher remission rate than patients taking a lower dose (10 mg) at 1 year[215] and 5 years[214] of follow-up.

Remission of symptoms

Remission of symptoms was defined as no symptoms in most studies, although some allowed mild symptoms. Higher doses of a proton pump inhibitor compared to a lower dose of the same drug resulted in more patients being symptom-free at study end, but again statistical analyses were not undertaken to compare the doses in most studies. Two studies of lansoprazole[207, 208] and 1 of omeprazole found no difference between the lower and higher doses.[211] With rabeprazole, the 1-year follow-up did not find a statistically significant difference between the doses, but the 5-year follow-up found the higher dose (30 mg daily) to be superior to the lower dose (15 mg daily).

Withdrawals

Differences in withdrawal (for any reason) rates were not apparent between the higher and lower doses in any of the studies.

Table 12. Proton pump inhibitors and treatment durations in longer-term studies of gastroesophageal reflux disease: Comparisons of standard doses with lower doses

Study	N	Duration	Initial short-term treatment (for healing)	Strategy 1	Strategy 2	Strategy 3
Robinson 1996	173	12 months	Lansoprazole 30 mg	Lansoprazole 30 mg	Lansoprazole 15 mg	Placebo
Sontag 1997	163	12 months	Lansoprazole 30 mg	Lansoprazole 30 mg	Lansoprazole 15 mg	Placebo
Hatlebakk 1997	103	12 months	Lansoprazole 30 mg	Lansoprazole 30 mg	Lansoprazole 15 mg	
Bate 1995	193	12 months	Omeprazole 20-40 mg	Omeprazole 20 mg	Omeprazole 10 mg	Placebo
Laursen 1995	168	6 months	Omeprazole 20-40 mg	Omeprazole 20 mg	Omeprazole 10 mg	Placebo
Caos 2000	209	12 months	Rabeprazole 10 or 20 mg	Rabeprazole 20 mg	Rabeprazole 10 mg	Placebo
Caos 2005[a]	497	5 years	Rabeprazole 10 or 20 mg	Rabeprazole 20 mg	Rabeprazole 10 mg	Placebo
Johnson 2001	318	6 months	Not reported	Esomeprazole 40 mg	Esomeprazole 20 mg	Esomeprazole 10 mg
Vakil 2001	375	6 months	Omeprazole 20 mg or esomeprazole 20 or 40 mg	Esomeprazole 40 mg	Esomeprazole 20 mg	Omeprazole 20 mg

[a] Extension of Caos 2000 and Birbara 2000.

Table 13. Remission of gastroesophageal reflux disease erosions and symptoms in longer-term studies of proton pump inhibitors: Comparisons of standard doses with lower doses

Study Year	Proton pump inhibitor	Percent of treatment group in remission (standard dose vs. low dose vs. placebo)[a]		
		Endoscopically confirmed remission	Symptom remission	Withdrawals
Robinson 1996	Lansoprazole	98% vs. 93% vs. 45% NS	67% vs. 72% vs. 35% NS	16% vs. 18% vs. 37%
Sontag 1996	Lansoprazole	94% vs. 86% vs. 13% NS	66% vs. 64% vs. 20% NS	30% vs. 70% placebo
Hatlebakk 1997	Lansoprazole	85% vs. 72% *P*=0.149	91.1% vs. 75% *P* value not reported	NR
Bate 1995	Omeprazole	74% vs. 50% vs. 14% NS	83% vs. 77% vs. 34% NS	NR
Laursen 1995	Omeprazole	59% vs. 35% vs. 0% *P* value NR	NR	3% vs. 6% vs. 12%
Caos 2000	Rabeprazole	**90% vs. 73% vs. 29%** ***P*<0.04**	90% vs. 73% vs. 29% NS	43% vs. 23% vs. 79%
Caos 2005	Rabeprazole	**89% vs. 77% vs. 37%** ***P*=0.005**	**61% vs. 52% vs. 22%** ***P*<0.05**	28% vs. 33% vs. 33%
Johnson 2001	Esomeprazole	93.6% vs. 93.2% vs. 57.1% vs. 29.0% *P* value not reported[a]	77.8% vs. 72.5% vs. 70.5% vs. 66.7% *P* value not reported	24% vs. 16% vs. 44% vs. 83%
Vakil 2001	Esomeprazole	88% vs. 79% vs. 54% vs. 29% *P* value NR	95% vs. 88% vs. 86% vs. 33% *P* value NR	27% in 40 mg group vs. 79% in placebo group; others NR

Abbreviations: NR, not reported; NS, not significant.
[a] Doses are listed in Table 9.
[a] *P* values for drug-drug comparisons not reported, *P* values for drug-placebo comparisons reported as *P*<0.001.

Standard-dose proton pump inhibitor compared with intermittent or 'on-demand' proton pump inhibitor

We identified 2 systematic reviews that compared intermittent or on-demand treatment to daily treatment for patients with gastroesophageal reflux disease.[218, 219] These reviews included studies of H2 receptor antagonists, studies comparing different doses of a proton pump inhibitor to one another, and different proton pump inhibitors with differing regimens (e.g. omeprazole given daily compared with esomeprazole given intermittently). Additionally, quality assessments of included studies were not undertaken. Most of the studies included in these reviews did not make a comparison between continuous (daily) proton pump inhibitor therapy and intermittent (3 times a week) or on-demand (taken daily when symptoms occur, discontinue when symptoms resolve) and were not included here. We have used these reviews only to identify additional studies not found in our literature searches.

Eight trials compared daily treatment with a proton pump inhibitor with intermittent or on-demand treatment of the same proton pump inhibitor.[208, 220-225, 226] One study followed patients for 1 year,[225] the rest followed patients for 6 months. Details of the study patients and

treatment strategies are presented in Table 14. In patients with healed endoscopically proven gastroesophageal reflux disease (Table 15), a regimen of daily proton pump inhibitor was superior to either 3 days a week or on-demand proton pump inhibitors of the same daily dose in preventing recurrence of erosive esophagitis based on endoscopy.[208, 221, 225] A 3-day-a-week regimen was also inferior to a daily regimen in preventing relapse of overall symptoms but no difference was found between daily treatment and on-demand treatment, although 1 study found that severity of heartburn was lower with the daily regimen.[221]

Table 14. Proton pump inhibitors and treatment durations in longer-term studies of gastroesophageal reflux disease: Comparisons of daily treatment with intermittent or on-demand treatment

Study	N	Diagnosis	Strategy 1	Strategy 2	Strategy 3
Sontag 1997	406	Healed erosive esophagitis	Omeprazole 20 mg daily	Omeprazole 20 mg 3 days a week	Placebo
Dent 1994	204	Healed erosive esophagitis	Omeprazole 20 mg daily	Omeprazole 20 mg 3 days a week	Ranitidine 300 mg daily
Sjostedt 2005	477	Healed erosive esophagitis	Esomeprazole 20 mg daily	Esomeprazole 20 mg on-demand	
Cibor 2006	65	NERD[a]	Lansoprazole 15 mg daily	Lansoprazole 30 mg on-demand	Lansoprazole 30 mg intermittent (4 weeks)
Bour 2005	181	NERD[a]	Rabeprazole 10 mg daily	Rabeprazole 10 mg on-demand	
Janssen 2005	432	NERD[a]	Pantoprazole 20 mg daily	Pantoprazole 20 mg on-demand	
Morgan 2007	268	Symptoms of gastroesophageal reflux disease	Rabeprazole 20 mg daily	Rabeprazole 20 mg on-demand	
Hansen 2005, 2006	1902	Symptoms of gastroesophageal reflux disease	Esomeprazole 20 mg daily	Esomeprazole 20 mg on-demand	Ranitidine 300 mg daily

Abbreviations: NERD, non-erosive reflux disease.
[a] Includes mild esophagitis grades 1 or A.

Table 15. Remission of gastroesophageal reflux disease erosions and symptoms in longer-term studies of proton pump inhibitors: Comparisons of daily treatment with intermittent or on-demand treatment

Study Year	Proton pump inhibitor	Comparison regimen	Percent of treatment group with result (daily vs. intermittent or on-demand regimen)	
			Endoscopically verified remission	Remission of symptoms
Healed erosive esophagitis				
Sontag 1997	Omeprazole	3 days a week	70% vs. 34% (*P*<0.001)	92% vs. 59% (*P*<0.001)
Dent 1994	Omeprazole	3 days a week	89% vs. 32% (*P*<0.001)	NR
Sjostedt 2005	Esomeprazole	On-demand	81% vs. 58% (*P*<0.0001)	95% vs. 94.3 (*P*=0.77)

In 3 studies of patients with endoscopically proven non-erosive esophagitis, no significant difference was found between daily and on-demand treatment with proton pump inhibitors rabeprazole or lansoprazole, in the severity of symptoms as measured on a visual analog scale at 3, 6, and 12 months,[222] or in the proportion with symptom relapse at 6 months.[224] Assessment of overall satisfaction with treatment was not different between regimens in 1 study[222] and final quality of life scores were also not different between groups in the other study.[224] However, the mean change in quality of life scores from baseline to 6 months was significantly better in the daily treatment group compared to the on-demand group (P=0.03).[224] The third study of pantoprazole 20 mg found the on-demand regimen to be noninferior to the daily regimen, based on the rates of 'treatment failure' defined as moderate symptoms for 3 or more days, use of > 1 dose of study medication on > 3 consecutive days, or withdrawal from study due to lack of efficacy.[226]

In patients presenting with symptoms of gastroesophageal reflux disease (but with no endoscopic examination), 2 studies found mixed results.[220, 227] In a study of on-demand esomeprazole, the results differ by which symptom-based outcome measure is used.[228] Statistical analyses of the results were not undertaken in the study, but here we have used a Yates corrected chi-square test. Using an outcome of "no heartburn" at 6 months, daily therapy is superior to on-demand treatment with 72% compared with 62% (P=0.002 using Yates corrected chi-square). However, the percentage of patients with no regurgitation at 6 months was 78% with daily therapy and 91% with on-demand treatment (P<0.001002 using Yates corrected chi-square). The other study found that daily treatment with rabeprazole resulted in statistically significantly more heartburn-free days (90%) compared with on-demand treatment (65%; P<0.0001) and fewer heartburn episodes (N=7 and 26, respectively; P<0.0001).These 2 studies also report different findings in quality of life. Again, the study of esomeprazole found the daily regimen superior to the on-demand regimen in both change from baseline in quality of life and patient satisfaction. However, data (including P values) supporting these claims are not clearly presented.[228] The other study found that on-demand treatment with rabeprazole resulted in greater improvement in quality of life at 6 months compared to the daily regimen.[220]

Standard-dose proton pump inhibitor compared with H2 receptor antagonist or placebo

Four studies found proton pump inhibitors to be superior to ranitidine 150 mg twice daily, 3 for prevention of relapse of healed esophagitis and 1 for prevention of recurrence of symptoms of gastroesophageal reflux disease.[229,230,223, 225] After 12 months, proton pump inhibitor therapy (pantoprazole 10 mg, 20 mg, or 40 mg and omeprazole 20 mg daily) resulted in lower relapse rates compared with ranitidine therapy. In 2 studies, more patients remained healed on pantoprazole at all doses than on ranitidine, and the rate of relapse was related to the dose of pantoprazole: Relapse occurred in 60%, 32%, and 18% of the 10 mg, 20 mg, and 40 mg groups, respectively. A second study of the same doses of pantoprazole and ranitidine found similar results.[230] During the first 12 months of maintenance treatment, healing was maintained in 78% of patients treated with pantoprazole 40 mg, 55% of patients treated with pantoprazole 20 mg, 46% of patients treated with pantoprazole 10 mg, and 21% of those treated with ranitidine. This study is planned for 3 years, but only the first 12 months have been reported so far. With omeprazole, at 12 months 89% remained in remission compared with 25% on ranitidine ($P<0.001$).[225] In those with symptoms suggestive of gastroesophageal reflux disease, 72% had relief of symptoms after 6 months of esomeprazole 20 mg daily compared with 33% taking ranitidine (statistical analysis not presented).

Additionally, a study of famotidine 20 mg twice daily compared with lansoprazole 15 mg daily, both as step down therapy from lansoprazole 30 mg daily for treatment of erosive esophagitis, found the proton pump inhibitor to be superior in preventing recurrence of regurgitation and heartburn, but not dysphagia or assessment of esophagitis grade after 8 weeks of maintenance treatment.[231] Fifty percent of patients taking famotidine experienced recurrence of heartburn, and 79% experienced recurrence of regurgitation compared to 0% and 7%, respectively, with lansoprazole 15 mg daily.

Comparison of esomeprazole administered orally compared to esomeprazole administered intravenously

A trial conducted in 246 ambulatory patients compared esophagitis healing rates at 4 weeks in patients given esomeprazole 40 mg either orally, via intravenous injection, or via intravenous infusion.[232] Patients were randomized to either 1 week of intravenous esomeprazole (injection or infusion) followed by 3 weeks of oral esomeprazole or 4 weeks of oral esomeprazole. The study was blinded using multiple placebos. After 4 weeks, there was no difference in healing rates among the 3 treatment groups (approximately 80%). The frequency and type of adverse events were also similar among the treatment groups.

Comparison of a reduced-dose proton pump inhibitor with an H2 receptor antagonist in children

One fair-quality randomized trial compared reduced-dose omeprazole with ranitidine for longer-term treatment of erosive gastroesophageal reflux disease in children (Evidence Table 6).[233] Children who had been treated with omeprazole and shown by endoscopy to be healed after 3 months began treatment with omeprazole 0.7 mg/kg daily (half the starting dose for the healing phase), ranitidine 10 mg/kg daily, or nothing for 6 months. Although no statistically significant difference was found among the groups at baseline, children in the group receiving no treatment had slightly less severe esophagitis and slightly lower symptom scores than children in the other groups. They were also slightly older at enrollment and at age of symptom onset. Follow-up

endoscopy at 3 months after the end of maintenance treatment was blinded. No statistically significant differences were seen in endoscopic or histologic grade or in symptom scores. One patient in the no treatment group had a relapse of erosive esophagitis (Hetzel and Dent grade 3). Twelve (25%) had mild symptoms at study endpoint and remained untreated, 6 in the no treatment group, 1 in the ranitidine group, and 5 in the omeprazole group. While the differences at baseline between the no treatment group and the drug groups may result in confounding results of those comparisons, there is no apparent difference between the drug groups in maintenance of remission of esophagitis and symptoms and in the number of patients requiring no further treatment.

Taper off proton pump inhibitor

A group of 97 patients with at least 8 weeks of daily use of a proton pump inhibitor with no history of peptic ulcer or esophagitis, and no evidence of esophagitis on endoscopy were enrolled in a 3 week trial of tapering the proton pump inhibitor dose prior to discontinuation or abrupt discontinuation.[234] In this study, patients were assigned to take omeprazole 20 mg daily for 3 weeks or to a blinded taper of omeprazole 20 mg daily for 1 week, 10 mg daily for 1 week, and 10 mg every other day for 1 week. Symptoms were assessed 1 week after discontinuation of drug, and the rate of resumption of proton pump inhibitor therapy was measured after 1 year. The mean duration of proton pump inhibitor treatment at study entry was 48 months. No statistically significant differences were found between tapering and non-tapering groups on symptom scores at 4 weeks, or the rate of resumption of treatment at 1 year.

Key Question 6. What is the comparative safety of different proton pump inhibitors in patients being treated for symptoms of gastroesophageal reflux disease, peptic ulcer, and nonsteroidal anti-inflammatory drug-induced ulcer?

Summary

- The comparative evidence on long-term adverse effects was limited. There was no long-term, head-to-head comparative studies (clinical or observational) specifically designed to monitor adverse effects.
- Two long-term (48 weeks to 5 years) maintenance studies found no difference between omeprazole and lansoprazole in adverse events or withdrawals due to adverse events, and a 6-month study comparing esomeprazole 20 mg with lansoprazole 15 mg found no difference in adverse event rates.
- In follow-up studies of individual drugs, no important differences in long-term findings were apparent, but comparisons across these studies are not clear.
- Short-term, head-to-head comparative studies indicate that the incidence of all and serious adverse events and the drop-out rate due to adverse events for all the proton pump inhibitors is low. No consistent differences between the proton pump inhibitors were seen in these trials.
- Evidence on long-term harms in children is limited. No serious adverse events were seen in observational studies. Serum gastrin levels were found to be elevated in >70% of children after 1 year of treatment regardless of which proton pump inhibitor was taken. Evidence on elevation of serum liver enzymes was more varied. A study of lansoprazole found elevated

aspartate aminotransferase in 4% of infants or neonates after 5 days of treatment for symptoms of gastroesophageal reflux.

- Studies indicated a potential for increased risk of clostridium difficile diarrhea associated with proton pump inhibitor use, but hospitalizations related to clostridium difficile diarrhea were not significantly associated.
- Evidence suggested an increased risk of osteoporotic bone fractures, including hip fracture, with longer duration exposure to proton pump inhibitors. However, 1 study found no association among patients with any major risk factors for fracture.
- Evidence on the association between community acquired pneumonia and proton pump inhibitor use was mixed.

Detailed Assessment

There were no head-to-head, long-term trials designed to compare adverse events between proton pump inhibitors. In long-term (6 months or longer) maintenance studies of patients with gastroesophageal reflux disease, there was no difference in the number of adverse events or number of withdrawals due to adverse events in the different proton pump inhibitor groups.[71, 78, 235] Reports of adverse effects in head-to-head comparisons of proton pump inhibitors for short-term treatment of gastroesophageal reflux disease and ulcer are shown in Evidence Table 12. The proportion of patients withdrawing due to adverse events in these studies was very low, with most studies reporting 1% to 3%. No study found significant differences among treatment groups in the rate of withdrawals for adverse effects. Reports of serious adverse events were uncommon and generally balanced among the drugs. Many of these incidences could be associated with preexisting diseases.

Several reports of long-term (ranging from 1 year up to 11 years) follow-up of individual proton pump inhibitors (omeprazole, lansoprazole, pantoprazole, and rabeprazole) have been published.[214, 225, 236-250] They studied potential adverse events including enterochromaffin-like cell hyperplasia, enterochromaffin-like cell carcinoids tumors, atrophic gastritis, intestinal metaplasia, N-nitrosamine formation (with overgrowth of gastric bacteria), enteric infections, malabsorption syndromes, and diarrhea. The risk of enteric infection may, rarely, be increased with sustained acid suppression.[251] The other concerns have not been observed in these long-term, noncomparative studies. While enterochromaffin-like cell hyperplasia has been seen to occur, no increased risk of enterochromaffin-like cell carcinoids has been observed. Likewise, atrophic gastritis is increased with long-term use of proton pump inhibitors, but progression to intestinal metaplasia and gastric cancer has not been shown. Overgrowth of gastric bacteria does occur, but a related higher rate of gastric adenocarcinoma has not been observed.

Using a pharmacovigilance database in Spain, the risk of adverse events (reported by organ system) was reported for each proton pump inhibitor compared to all other drugs in the database (Table 16).[252] Using this analysis, increased risk of adverse events were found associated with specific proton pump inhibitors, as below. The authors note “A direct relationship was found between consumption and the number of reports.” Without controlling for this difference in the analysis, these results should be interpreted cautiously.

Table 16. Risk of adverse events for proton pump inhibitors compared with other ulcer drugs (Salgueiro 2006)[252]

Adverse event by organ system	Proton pump inhibitor	Odds ratio (95% CI)
Skin and appendage disorders	Omeprazole Rabeprazole	1.4 (1.2 – 1.7) 1.9 (1.1 – 3.2)
Urinary system	Lansoprazole	2.7 (1.2 – 6.2)
Reproductive female	Lansoprazole	4.2 (1.5 – 11.4)
Endocrine disorders	Lansoprazole	4.0 (1.3 – 12.7)
Liver and biliary system disorders	Lansoprazole Pantoprazole	2.4 (1.1 – 5.1) 3.0 (1.7 – 5.5)
Musculoskeletal system disorders	Esomeprazole Omeprazole	2.9 (1.2 – 7.4) 1.8 (1.3 – 2.4)
Vision disorders	Pantoprazole Rabeprazole Esomeprazole	3.0 (1.5 – 6.1) 4.0 (1.6 – 10.0) 3.4 (1.1 – 11.1)
Gastrointestinal system disorders	Omeprazole Lansoprazole	1.8 (1.5 – 2.1) 2.4 (1.6 – 3.7)

Diarrhea

A nested case-control study of 10 008 lansoprazole users followed for 4 years found a dose-related trend for diarrhea (5%, 4%, and 3% of patients using 60 mg or more, 30 mg, and 15 mg or less, respectively; P=0.08).[248] In 42% of patients reporting diarrhea the lansoprazole dosage was reduced or discontinued as a response. Cases had a higher current use of oral antibiotics than controls with no diarrhea (adjusted odds ratio, 2.7; 95% CI 1.0 to 6.9).

Two case control studies examined the relationship between clostridium difficile associated diarrhea and acid suppression, including proton pump inhibitors.[253, 254] The first, based on 1672 cases and 16720 controls, found a significantly increased risk of community acquired clostridium difficile diarrhea in patients who were currently using a proton pump inhibitor (relative risk 2.9; 95% CI 2.4 to 3.4).[253] However, the second, based on 1389 cases and 12303 controls, did not find a significant association between hospitalization due to clostridium difficile diarrhea and exposure to a proton pump inhibitor within 90 days (odds ratio 0.0.9; 95% CI 0.8 to 1.1).[254] Neither study examined differences between proton pump inhibitors.

Bone fractures

Four nested case control studies examined the association between exposure to proton pump inhibitors and risk of fracture.[255-258] Three of the studies found statistically significant increased risk of fracture associated with proton pump inhibitor use, although they differed in the duration of exposure that was found significantly associated with increased risk. The largest included 124 655 cases and 373 962 controls drawn from Danish registers of National Board of Health, the Danish Medicines Agency, and the National Bureau of Statistics.[256] Cases included any patient with a fracture in the year 2000. An increased risk of *any fracture* was associated with last use of a proton pump inhibitor within 1 year of the index date (adjusted odds ratio 1.18; 95% CI 1.12 to 1.43). Exposure that ended more than 1 year prior to the fracture was not significantly associated,

and a dose-response effect was not found. Cumulative dose was used as a proxy for duration of exposure, and the increased risk was found to be similar across exposure groups (≤ 25, 26-99 and ≥ 100 defined daily dosages). Similar results were found for specific fracture sites (hip, forearm and spine). This study controlled for exposure to multiple drug classes, but was not able to control for calcium or vitamin D and did not differentiate types of fracture.

In contrast, 2 studies involving 13 566 and 15 792 cases found increased risk based on duration and dose of proton pump inhibitor use in patients 50 years and older.[255, 257] One identified patients older than 50 years, who had been exposed to a proton pump inhibitor for at least 1 year prior to the index date (date of hip fracture). After 1 year of use, an increased risk was found; adjusted odds ratio of 1.44 (95% CI 1.30 to 1.59), increasing by year to 1.59 (95% CI 1.39 to 1.80) at 4 years of use.[255] The risk increased again with higher daily dosages of proton pump inhibitor, with adjusted odds ratios of 1.40 (95% CI 1.26 to 1.54) for those using ≤ 1.75 average daily doses, and 2.65 (95% CI 1.80 to 3.90) for those using ≥ 1.75 average daily doses. Multiple potential confounding factors were controlled for; including several groups of drugs know to influence bone metabolism, including calcium or vitamin D. The second study included patients with vertebral, wrist or hip fractures, again controlling for multiple potential confounders, including drugs (but not calcium or vitamin D).[257] No increase in risk was found with durations of exposure up to 6 years. The risk for any osteoporotic fracture was increased only with 7 or more years of exposure (adjusted odds ratio 1.92; 95% CI 1.16 to 3.18). The risk of hip fracture alone was increased after 5 years of exposure (adjusted odds ratio 1.62; 95% CI 1.02 to 2.58) although the magnitude of risk increased again with 6 and 7 years of exposure.

The fourth study limited the population of cases and controls to those with no major risk for hip fracture.[258] With 1098 cases and 10 923 controls, this was the smallest study. No association was found between proton pump inhibitors and incidence of hip fractures. The estimated relative risk of hip fracture for those who received *one or more* proton pump inhibitor prescriptions before the index date was 0.9 (95% CI 0.7 to 1.1), compared with those who received no prescriptions. This study also evaluated individual proton pump inhibitors and found similar results for each drug. The discordant results of this study compared to the other 3 may be due to smaller numbers and a differing selection process in that patients with as little as 1 prescription for a proton pump inhibitor were included and further stratification of exposure or dose were not undertaken.

Community acquired pneumonia

Two studies examined the association between proton pump inhibitor use and community acquired pneumonia, coming to somewhat different conclusions.[259, 260] A large, good-quality nested case-control study identified 80 066 cases and 799 881 controls drawn from a cohort of patients from a general practice research database.[260] The adjusted odds ration for the association of recent (within 30 days) use of a proton pump inhibitor and a diagnosis of community acquired pneumonia was 1.02 (0.97–1.08). This study did find, however, that the risk was significantly increased if the patient had started the proton pump inhibitor within 2 or 14 days, but not with longer durations of therapy. The other study, fair quality, identified 475 cases and 4960 controls from a cohort of patients who had all been exposed to an acid reducing drug during the study period.[259] The exposure was then stratified into recent (within 30 days) or past (>30 days since exposure). This study found an increased risk among current users of a proton pump inhibitor, with an adjusted relative risk of 1.89 (95% CI 1.36 to 2.62) compared to those who had stopped taking a proton pump inhibitor 30 or more days ago.[259] This study did report an analysis of each

proton pump inhibitor with enough cases to conduct an analysis, finding an increased risk with omeprazole and pantoprazole, adjusted odds ratios 1.74 (95% CI 1.28 to 2.35) and 2.29 (95% CI 1.43 to 3.68), respectively, but not with lansoprazole 0.91 (95% CI 0.35 to 2.34). However, because there were few cases for each drug, these results should be interpreted with caution.

A study combining data from all Phase II-IV trials of esomeprazole examined the risk of respiratory tract infections in 16 583 patients assigned to esomeprazole and 12 044 assigned to placebo or other acid suppressing drugs.[261] Compared to placebo, this analysis did not find a difference in risk of any respiratory tract infection (relative risk 0.93; 99% CI 0.78 to 1.11); lower respiratory tract infection (relative risk 0.92; 99% CI 0.59 to 1.42); or pneumonia (relative risk 0.94; 99% CI 0.29 to 3.07). Analyses of the relative risk with esomeprazole compared with omeprazole, lansoprazole, or ranitidine did not indicate statistically significant differences. Because this is a pooled analysis of selected studies without a systematic review, the quality of this study is undetermined and the results should be interpreted with caution.

Colorectal cancer

A nested case control study of 4432 cases and 44 292 controls from the General Practice Research Database (UK) evaluated the association between duration of proton pump inhibitor use and incidence of colorectal cancer.[262] While multiple durations of exposure were examined, the one showing a statistically significant increased risk was diagnosis of colorectal cancer with less than 1 year exposure to a proton pump inhibitor with an adjusted odds ratio of 2.6 (95% CI 2.3 to 2.9). Less than 1 year of exposure, more than 12 months prior to the index date, and 1 to 2, 2 to 3, 3 to 4, 4 to 5, or >5 years of proton pump inhibitor use were not statistically significantly associated with colorectal cancer. The adjusted odds ratio for ≥5 years of proton pump inhibitor exposure was 1.1 (95% CI 0.7 to 1.9). Among high-dose proton pump inhibitor users (≥1.5 defined daily doses/day), there was a nonstatistically significant trend toward an increased risk with increasing duration of use (test for trend, P=0.2).

Serum gastrin levels

Serum gastrin level were monitored in several studies and found to be significantly elevated above baseline although the magnitude of increase was small and generally not considered clinically significant. A dose-related difference was found in some studies, but there were no differences between different proton pump inhibitors. Likewise, when studied, the effect of different proton pump inhibitors on *Helicobacter pylori*-related gastritis was similar, worsening gastritis in the corpus and improving gastritis in the antrum.[263]

Adverse events in children

Reporting of adverse events in children was limited to short-term trials and 2 open-label uncontrolled studies with longer follow-up.[264, 87, 88, 188, 189, 209-212 265] In short-term trials of omeprazole no serious adverse events were reported.[87, 209, 214]

Lansoprazole was studied in infants and neonates in 2 similar trials of children with symptoms of gastroesophageal reflux disease. [265] The infants, age > 28 days by but < 1 year, were given a suspension of lansoprazole dosed at 1 or 2 mg/kg/day and the neonates (up to 28 days after birth) were given 0.5 to 1.0 mg/kg/day for 5 days. Twenty-four neonates and 24 infants were enrolled. Mean age in the infant group was 24 weeks, and 3.7 weeks in the neonate group. While most neonates were white, 50% of the infants were black. While a large number of

adverse events were reported (58%) 4 in the neonates (8%), and 1 in the infant group (4%) were considered related to the drug. In neonates, the adverse events were anemia, flushing (2 patients), and elevated aspartate aminotransferase level and were considered mild or moderate in severity. One infant also had elevated an aspartate aminotransferase level. The increases in aspartate aminotransferase occurred in the higher dose groups for each age group (0.5 and 2.0 mg/kg/day, respectively).

A retrospective chart review of 113 children identified from a registry-type database examined children with erosive esophagitis who received a proton pump inhibitor for at least 1 year.[264] The majority (66%) was taking lansoprazole, followed by omeprazole (22%), and few were taking pantoprazole, rabeprazole, or esomeprazole. Overall, 88% of the children had no adverse event while taking a proton pump inhibitor, with a range of 80% to 100% for specific proton pump inhibitors. The most frequent adverse events recorded in patients' charts were constipation (4%) and diarrhea (5%). Serum gastrin level was elevated (>90 pg/mL) in 73% of children, with no statistically significant differences by specific proton pump inhibitor, dose, dosing frequency, or treatment duration. No elevation in liver enzymes was reported.

In a before-after study of omeprazole for esophageal reflux, 15 children were followed for a mean of 12 months. Seven (47%) had elevation of liver enzymes. Eleven (73%) had hypergastrinemia.[213] A short-term before-after study of pantoprazole reported elevated liver enzymes in 1 of 18 children exposed for 28 days and 5 of 18 (28%) had hypergastrinemia.[211] In a 2-week study of lansoprazole in children (mean age 11 years) only mild gastric adverse events were reported.[212]

Two short-term trials compared lower dose and higher dose esomeprazole in children with gastroesophageal reflux disease. These trials made no comparison to placebo or other drugs. In 148 adolescents aged 12 to 17 years assigned 20 or 40 mg esomeprazole daily for 8 weeks, 15% experienced an adverse event considered related to esomeprazole; headache (8%), abdominal pain (3%), nausea (2%), and diarrhea (2%).[266] In 108 younger children, aged 1 to 11 years, who were assigned to 5 or 10 mg esomeprazole if weight < 20 Kg or 10 or 20 mg if weight > 20 Kg, 9% reported an adverse event considered related to esomeprazole; diarrhea (2.8%), headache (1.9%), and somnolence (1.9%).[267] Serious adverse events thought to be related to esomeprazole were not reported in either study.

Key Question 7. Are there subgroups of patients based on demographics, other medications, or comorbidities for which a particular medication or preparation is more effective or associated with fewer adverse effects?

Summary

- Head-to-head comparison studies did not adequately describe or analyze subgroups for differences in effectiveness. However, 2 studies assessed adverse effects in subgroups of age, gender, and race and found no difference among groups.
- Studies suggested that a lower dose of proton pump inhibitor may be equally effective in patients who are older or are deficient in the CYP2C19 liver enzyme (3% of whites and African Americans and 17% to 25% of Asians). Only 1 of these studies was a head-to-head comparison, omeprazole compared with lansoprazole, but no difference was found between the drugs.

- While the effects of the proton pump inhibitors may differ by demographics, there was inadequate data to identify any of these differences.
- Based on a cohort study of more than 8000 patients, use of a proton pump inhibitor concomitant with clopidogrel following acute coronary syndrome increased the risk of death or rehospitalization for acute coronary syndrome with adjusted odds ratio of 1.25 (95% CI 1.11 to 1.41).
    - Similarly, use of a proton pump inhibitor concomitant with clopidogrel following acute myocardial infarction can increase the risk of readmission for recurrent myocardial infarction within 90 days with adjusted odds ratio 1.27 (95% CI 1.03 to 1.57) based on a smaller nested case-control study of 734 cases and 2057 controls. Analysis of the subgroup taking pantoprazole indicated no increased risk, while analysis of the other proton pump inhibitors (as a group) indicated a similar increase in risk.

Detailed Assessment

Age and sex

In included head-to-head studies, the enrolled patients were middle aged, with mean ages ranging from 43[268] to 70[162] years. From 38% to 89% of the patients were male. The ethnicity of participants was stated in only 5 trials.[4, 25, 75, 108, 268] The majority of studies included mostly white populations. In those studies with greater variation subgroups were too small for meaningful analyses by racial or ethnic group.

An open-label, single-center trial conducted in 320 patients over age 65 compared 4 proton pump inhibitors for healing and symptom resolution in erosive esophagitis.[269] This was the only head-to-head trial conducted exclusively in elderly patients. The mean age of the group was 77.4 years (standard deviation 7.9 years, range 65-93 years). Nineteen patients withdrew from the study (5.9%), 2 due to adverse events. Patients were randomized to omeprazole 20 mg, lansoprazole 30 mg, pantoprazole 40 mg, or rabeprazole 20 mg. After 8 weeks of treatment, the healing rate in the overall group was 85% (intention-to-treat). Healing rates in the pantoprazole (90%) and rabeprazole (89%) groups were significantly higher than the omeprazole group (75%; P=0.022 and P=0.040, respectively). No difference was found between omeprazole and lansoprazole (75% and 85%; P=NS). Pantoprazole and rabeprazole were also superior to omeprazole and to lansoprazole for resolution of heartburn (rates 100% for pantoprazole and rabeprazole, 87% for omeprazole, and 82% for lansoprazole). The frequency of adverse events was low (4 patients; 1.3%), and there were no differences between treatment groups in the prevalence of adverse events.

There was 1 small, 12-month, placebo-controlled trial in which pantoprazole 20 mg was effective for maintenance treatment of gastroesophageal reflux disease in patients age 65 or older.[270] An age-based analysis of healing or prevention was not possible in most head-to-head trials, due to the small numbers of older patients. However, 2 trials did assess the impact of age, gender, and race on the incidence of adverse effects.[5, 106] There were no differences between proton pump inhibitors (omeprazole, rabeprazole, esomeprazole) on the basis of these characteristics. The effect of age on eradication rate was also evaluated.[198] This study found higher eradication rates among patients older than 50 years than patients younger than 50, but proton pump inhibitors were not compared.

In trials comparing a proton pump inhibitor with another drug, the same general statements can be made, but a few findings deserve comment. Studies looking at healing or prevention of nonsteroidal anti-inflammatory drug-induced ulcer included more women than men, with the proportion of women ranging from 62% to 67% and 64% to 83% in the respective types of study. This is most likely due to the greater prevalence among women of diseases requiring long-term nonsteroidal anti-inflammatory drug treatment. However, no gender-based analyses were presented.

Genotype

The proton pump inhibitors are all metabolized, largely by the CYP2C19 and CYP3A4 liver enzymes. Theses enzymes are estimated to be deficient in 3% of white and African Americans and 17% to 25% of Asians. The deficiency results in a significantly longer half-life of proton pump inhibitors, although clinically significant accumulation of these drugs has not been shown. While dose adjustments are not required, and adverse effect profiles of the drugs do not differ, there is some evidence that lower doses may be effective in these populations[184, 271] and that rapid metabolizers may have a higher rate of failure to eradicate *Helicobacter pylori*[176, 177, 187] and to heal esophagitis.[272] Subgroup analysis found no effect by race in 1 study of esomeprazole and lansoprazole in healing of erosive esophagitis.[4] A small study (N=80) found no statistically significant difference at 8 weeks in rate of ulcer healing between rabeprazole 10 mg daily and omeprazole 20 mg daily among patients with differing CYP2C19 genotype.[108] The few adverse events were not analyzed by genotype. A trial of omeprazole in Japanese patients with recurrent esophagitis found no difference in efficacy or safety by genotype.[273]

Older patients also metabolize proton pump inhibitors more slowly, resulting in significantly higher drug levels and half-lifes. However, accumulation has not been shown, and dose adjustments are not recommended. One reanalysis of data from 2 trials comparing omeprazole with either ranitidine or cimetidine for reflux esophagitis compared effect in patients age 65 or older with those under age 65.[274] In this analysis there was no difference in healing rate or symptom resolution at 4 or 8 weeks, with a slightly higher proportion of older patients both healed and symptom-free. Withdrawals due to adverse event were higher in the older group, 7.6% compared with 2.5%. Similar data are not available for other proton pump inhibitors.

Comorbidity

In an uncontrolled, non-randomized open-label study, patients with peptic ulcer and comorbid liver disease were given 6 to 8 weeks of rabeprazole 10 mg to 20 mg.[275] Eleven of 108 patients (10%) reported 21 adverse drug events, resulting in 5 withdrawals (5%) and an additional 5 patients with an adverse event were lost to follow up. Two patients (2%) had adverse events that were rated as serious, 1 had an elevated bilirubin level, and the other had hepatic encephalopathy. Analysis by dose was not conducted.

Concomitant medications

Two good quality observational studies assessed the impact of a potential drug interaction between proton pump inhibitors and clopidogrel following an acute coronary syndrome (ACS).[276, 277] Clopidogrel is activated by a liver enzyme system known as P450 C19, and proton pump inhibitors can inhibit this system. A cohort study of 8205 patients who were discharged after an ACS and were prescribed clopidogrel between October 2003 and January 2006 were examined to

determine if the rate of death or rehospitalization for ACS was affected by concomitant use of a proton pump inhibitor.[276] Of these patients, 64% were prescribed a proton pump inhibitor. Multivariable analysis found that there was an increased risk of death or rehospitalization for ACS in those patients taking both clopidogrel and a proton pump inhibitor; adjusted odds ratio 1.25 (95% CI 1.11 to 1.41). The analysis controlled for multiple variables, included demographic characteristics, comorbidities, previous cardiac history, and other medications. In patients who had period with and without a proton pump inhibitor, but continued clopidogrel use, the risk of the primary outcome was also increased during the proton pump inhibitor periods; adjusted odds ratio 1.27 (95% CI 1.10 to 1.46). In addition to the primary outcome, secondary outcomes were evaluated. The risk of rehospitalization for ACS was increased (adjusted odds ratio 1.86 95% CI 1.57 to 2.20); the risk of a revascularization procedure was increased (adjusted odds ratio 1.49 95% CI 1.30 to 1.71); however risk of all-cause mortality was not significantly increased (adjusted odds ratio 0.91 95% CI 0.80 to 1.05). The authors also conducted a nested case-control analysis with these data in an attempt to confirm their findings, resulting in an adjusted odds ratio of 1.32 (95% CI 1.1.4 to 1.54) for the risk of death or rehospitalization for ACS. Multiple sensitivity analyses were conducted, with no meaningful change to the results. This study was conducted using data from the Veteran's Affairs hospitals, and no patients were taking esomeprazole. Too few patients were taking pantoprazole or lansoprazole to be able to conduct individual analyses, but omeprazole and rabeprazole resulted in increased adjusted odds ratios for the primary outcome (adjusted odds ratios: 1.24 95% CI 1.08 to 1.41 for omeprazole, N=3132; 2.83 95% CI 1.96 to 4.04, N=151 for rabeprazole). Analysis by dose of proton pump inhibitor indicated did not indicate a dose-response relationship.

A population-based nested case-control study examined data from all patients in Ontario, Canada who were prescribed clopidogrel after hospital discharge following a myocardial infarction between April 2002 and December 2007.[277] In this study, 13 636 patients were identified. Among this group, cases were identified as patients who were rehospitalized for myocardial infarction within 90 days of discharge (N=734), while controls were those who were not. Controls were identified in a 3:1 ratio to cases and matched on age, percutaneous coronary intervention, and a validated risk score (N=2057). Proton pump inhibitor exposure was defined as current (within 30 days of rehospitalization), previous (31 to 90 days) or remote (91 to 180 days). The logistic regression analysis controlled for demographic variables, socioeconomic status, Charlson comorbidity index, length of stay during initial admission for myocardial infarction, and 9 comorbid conditions (for example diabetes). A similar adjusted odds ratio was found in this study as the cohort study; 1.27 (95% CI 1.03 to 1.57) for current users of a proton pump inhibitor. Previous or remote use was not associated with an increased risk of recurrent myocardial infarction. All-cause mortality was again not affected statistically significantly (adjusted odds ratio 0.82 95% CI 0.57 to 1.18). Analysis of recurrent myocardial infarction within 1 year of initial discharge also indicated an increased risk with current proton pump inhibitor use; odds ratio 1.23 (95% CI 1.01 to 1.49). Because pantoprazole does not inhibit the P450 2C19 enzyme system responsible for activation of clopidogrel, it has been suggested that it may not result in a clinically-relevant drug interaction. An analysis of pantoprazole alone (N=cases 46, controls 125) found no statistically significant increase in risk (adjusted odds ratio 1.02 95% CI 0.70 to 1.47). Analysis of all other proton pump inhibitors (which inhibit the P450 2C19 enzyme system to varying degrees) together resulted in increased risk; adjusted odds ratio 1.40 (95% CI 1.10 to 1.77; N=cases 148, controls 299). Analysis stratified further by individual proton pump inhibitor was not undertaken; insufficient data may have prevented such analysis.

Because these are post-hoc sub-group analyses of small groups, further research is needed to confirm these findings.

Pregnancy

A multicenter, prospective cohort study enrolled 410 pregnant women who had sought counseling after exposure to omeprazole (N=295), lansoprazole (N=62), or pantoprazole (N=53) between 1992 and 2001.[278] Details of exposure were collected during pregnancy before pregnancy outcome was known, and follow-up was performed in the neonatal period. A control group of 868 women who had been counseled during pregnancy about exposures known to be nonteratogenic served as a control group. There were some differences between control and treatment groups at baseline (for example, number of children was larger in then treatment than the control group), and confounders were not controlled for in the analysis. There was a higher rate of elective termination of pregnancy in the omeprazole and lansoprazole groups than the control group. Two of these terminations in the omeprazole group, 1 in the lansoprazole group, 0 in the pantoprazole group, and 5 in the control group were because of prenatal diagnosis of anomalies. There was no difference in the rate of major anomaly between each of the 3 groups and the control group; the relative risk was 0.95 (95% CI 0.46 to 1.98) for omeprazole, 1.04 (95% CI 0.25 to 4.21) for lansoprazole, and 0.55 (95% CI 0.08 to 3.95) for pantoprazole. Median birth weight was lower by 60 grams in the omeprazole group than the control group, but no difference was seen between groups for median gestational age at delivery or rates of preterm birth, miscarriage, ectopic pregnancy, or stillbirth.

Applicability

Applicability of most trials to community practice was difficult to determine. These studies generally excluded patients who had serious medical conditions. In addition, although most treatment and control groups received standard doses of anti-ulcer drug, there were instances where doses were higher or lower than typical. In trials comparing maintenance treatment or different strategies for longer-term treatment of gastroesophageal reflux disease, patients were enrolled on the basis of a successful response to acute treatment. This preselection may have resulted in a group of patients who were adherent to treatment, who were able to tolerate any side effects, and whose disease was less severe in comparison with patients who were not enrolled. Another concern is that of studies that stated their funding source, most were funded by the pharmaceutical industry, and industry employees often served as co-authors.

SUMMARY

Table 17 summarizes the evidence for this report.

Table 1. Summary table

Key Question	Strength of evidence	Conclusion
Key Question 1. Gastroesophageal reflux disease, short-term efficacy		
Erosive gastroesophageal reflux disease: Symptoms	Good	In 16 head-to-head trials, the only difference between proton pump inhibitors on the outcome of complete

Key Question	Strength of evidence	Conclusion
		symptom relief at 4 weeks was in the comparison of esomeprazole 40 mg with omeprazole 20 mg; the pooled risk difference in 3 trials was 8% (95% CI 3 to 13), with a number needed to treat of 13. Time to relief of heartburn was similar for all proton pump inhibitors in head-to-head trials, but the methods used to measure and report this outcome varied in the 14 studies.
Erosive gastroesophageal reflux disease: Esophagitis healing	Good	Good evidence shows no difference between omeprazole, lansoprazole, pantoprazole, and rabeprazole for healing of esophagitis. Thirteen head-to-head trials found these 4 proton pump inhibitors to be equally effective in healing at 4 and 8 weeks. Pooled analysis of 4- and 8-week healing rates from 4 trials of esomeprazole 40 mg compared to omeprazole 20 mg indicate esomeprazole to be superior; risk difference 7% (95% CI 1 to 12) and a number needed to treat of 14 and 5% (95% CI 1 to 9), number needed to treat = 20, respectively. Three trials compared esomeprazole 40 mg with lansoprazole 30 mg. The pooled difference in healing rate was significantly greater with esomeprazole at 4 and 8 weeks, risk differences 5% (95% CI 2 to 7) and 3% (95% CI 1 to 5), respectively. Four trials compared esomeprazole 40 mg and pantoprazole 40 mg. Pooled difference in healing rate was significantly greater with esomeprazole at 4 weeks, but not at 8 weeks, risk differences 5% (95% CI 2 to 8) and 1% (95% CI –3 to 5).
Healing in moderate to severe erosive esophagitis	Fair	Esomeprazole 40 mg was more effective at healing esophagitis at 4 and 8 weeks than omeprazole 20 mg and lansoprazole 30 mg. The pooled risk difference in 3 studies comparing omeprazole 20 mg with esomeprazole 40 mg was 16% at 4 weeks and 13% at 8 weeks (number needed to treat = 6 at 4 weeks, 8 at 8 weeks).The pooled risk difference in 2 studies comparing lansoprazole 30 mg with esomeprazole 40 mg was 8% at 4 weeks and 9% at 8 weeks (number needed to treat = 13 at 4 weeks, 11 at 8 weeks). Evidence is mixed on differences between esomeprazole 40 mg and pantoprazole 40 mg. At 4 weeks, esomeprazole 40 mg had a higher healing rate \than pantoprazole 40 mg - pooled risk difference (2 studies), 14% (95% CI 7 to 20). At 8 weeks, no difference was found in a single small study. Lansoprazole 30 mg (2 studies) and esomeprazole 20 mg (1 study) were no different to omeprazole 20 mg at 4 or 8 weeks.
Erosive gastroesophageal reflux disease: Prevention of relapse	Good	For maintenance of healed esophagitis, there is good evidence that no difference exists between omeprazole, lansoprazole, and rabeprazole. The longest study (over 5 years) compared omeprazole with rabeprazole. No difference was found between esomeprazole 20 mg and pantoprazole 20 mg in combined symptomatic and endoscopic remission rates after 6 months. Esomeprazole 20 mg was found to have lower relapse rates than pantoprazole 20 mg in 2 6-month studies.
Non-erosive or empirically-treated gastroesophageal reflux	Fair	Three head-to-head trials in patients with endoscopy-negative gastroesophageal reflux disease found no

Key Question	Strength of evidence	Conclusion
disease: Symptoms		difference between esomeprazole 20 mg and omeprazole 20 mg, pantoprazole 20 mg, and rabeprazole 10 mg. These studies used different outcome measures. Limited indirect evidence from placebo- and active-controlled trials suggests similar efficacy for heartburn resolution and complete symptom relief for the 5 proton pump inhibitors.
Non-erosive or empirically-treated gastroesophageal reflux disease: Prevention of relapse	Fair to Poor	In a 6-month head-to-head trial of on-demand esomeprazole compared with daily lansoprazole 15 mg, more patients discontinued lansoprazole.. On-demand rabeprazole 10 mg, on-demand esomeprazole 20 mg, and daily omeprazole 10 mg were more effective than placebo in prevention of relapse of symptoms over 6 months in patients with endoscopy negative gastroesophageal reflux disease.
Gastroesophageal reflux disease: Evidence in Children	Poor	There are no direct comparisons of proton pump inhibitors for reflux esophagitis in children. A fair quality placebo-controlled trial in infants did not find omeprazole to be superior to placebo.
Key Questions 2, 3, 4. Peptic ulcer, *Helicobacter pylori* eradication		
Duodenal Ulcer	Fair	All newer proton pump inhibitors have been compared to omeprazole. The evidence from 10 head to head trials suggests no difference between the proton pump inhibitors in healing rates or symptom relief.
Gastric Ulcer	Fair	Three head-to-head studies were found, comparing rabeprazole to omeprazole. No significant differences in healing rate was found. Minor improvements in symptom relief were found with a higher dose of rabeprazole (20 mg) compared to omeprazole 20 mg, but not with a lower dose (rabeprazole 10 mg). There are no other direct comparisons.
Nonsteroidal anti-inflammatory drug-induced ulcer	Poor	No head-to-head studies. In trials of omeprazole and lansoprazole compared with ranitidine, no difference in healing rates or symptom resolution rates were apparent.
Prevention of nonsteroidal anti-inflammatory drug induced ulcer	Poor	Direct comparison of pantoprazole 20 mg, 40 mg and omeprazole 20 mg daily did not indicate statistically significant differences in rates of therapeutic or endoscopic failure at 6 months in a group of patients taking nonsteroidal anti-inflammatory drugs regularly for arthritic conditions. There are no other direct comparisons.
Eradication of *Helicobacter pylori*	Fair	Five fair quality systematic reviews and 29 more recent trials indicate that eradication rates among the proton pump inhibitors do not differ significantly. Pooled analysis of eradication rates stratified by number of days of treatment and dose comparison did not find statistically significant differences in eradication rate among the proton pump inhibitors. Differences between the antibiotic regimens, participants and study designs limit the strength of this evidence. In children, evidence is extremely limited, with only 2 trials of lansoprazole versus placebo. Neither trial found the addition of lansoprazole to result in higher eradication rates than antibiotic therapy alone.

Key Question	Strength of evidence	Conclusion
Key Question 5. Dosing strategies for maintenance therapy in gastroesophageal reflux disease		
Standard dose compared with low-dose proton pump inhibitor	Good	Based on 11 studies, time in remission was longer for higher doses compared with lower doses for omeprazole and rabeprazole, but the same for higher and lower doses of lansoprazole. Evidence on esomeprazole was inconclusive. Rates of endoscopically verified remission at study end were greater with the higher dose of rabeprazole compared with the lower dose, but no different between dose strategies for omeprazole and lansoprazole. Rates of relapse of symptoms were generally higher with lower doses of omeprazole, lansoprazole, and rabeprazole.
Standard dose compared with intermittent or on-demand proton pump inhibitor	Fair	In 3 studies of patients with healed erosive esophagitis, a regimen of daily proton pump inhibitor was superior in preventing relapse of esophagitis or recurrence of symptoms compared with 3 days a week or on-demand regimens at 6 months. In 3 studies of patients with nonerosive esophagitis, assessments of symptom severity or relapse of symptoms was not different between daily and on-demand regimens. Patient satisfaction and quality of life ratings at study end were also not different, although the mean change in quality of life score from baseline was better with daily therapy. In 2 studies of patients presenting with symptoms of gastroesophageal reflux disease, but without endoscopic assessment, evidence is mixed.
Proton pump inhibitor compared with H2 receptor antagonist	Fair	Daily proton pump inhibitor therapy was found superior to daily H2 antagonist therapy (rantidine 300 mg daily) in preventing relapse of erosive esophagitis, or symptoms of gastroesophageal reflux disease in 4 studies. In children, at 3 months omeprazole 0.7 mg/kg daily was not different to ranitidine 10 mg/kg daily or placebo.
Key Question 6. Adverse events		
Long-term studies	Comparative evidence = Poor	Three comparative trials. Evidence from single-drug follow-up studies indicates no differences between the proton pump inhibitors. A pharmacovigilance study found increased risk of adverse events related to specific PPIs – study limitations indicate a need for further study. Noncomparative evidence indicates a potential for increased risk of colorectal cancer (1 study), clostridium difficile diarrhea (2 studies), and fracture (4 studies). Mixed evidence was found on the risk of community acquired pneumonia with proton pump inhibitor use.
Short-term studies	Fair	Evidence from short-term head-to-head comparison trials does not indicate a difference in the rate of overall adverse events, serious adverse events or the rate of dropouts due to adverse events. These studies are very short-term and include highly selected patient populations; evidence may not be generalizable to patients with co-morbidities and longer-term treatment.

Key Question	Strength of evidence	Conclusion
Key Question 7. Subpopulations		
	Fair	2 studies found no difference in adverse effects in subgroups of age, gender, and racial groups A single open-label study of 320 patients with mean age of 77 years with erosive esophagitis found that that pantoprazole 40 mg and rabeprazole 20 mg were superior to omeprazole 20 mg in healing rate at 8 weeks, no difference compared to lansoprazole 30 mg. Pantoprazole and rabeprazole were superior to both omeprazole and lansoprazole in symptom relief at 8 weeks. These results differ to those found in younger populations and need confirmation. Based on a cohort study of more than 8000 patients, use of a proton pump inhibitor concomitant with clopidogrel following acute coronary syndrome can increase the risk of death or rehospitalization for acute coronary syndrome with adjusted odds ratio of 1.25 (95% CI 1.11 to 1.41). Similarly, use of a proton pump inhibitor concomitant with clopidogrel following acute myocardial infarction can increase the risk of readmission for recurrent myocardial infarction within 90 days with adjusted odds ratio 1.27 (95% CI 1.03 to 1.57) based on a smaller nested case-control study of 734 cases and 2057 controls. Analysis of the subgroup taking pantoprazole indicated no increased risk, while analysis of the other proton pump inhibitors (as a group) indicated a similar increase in risk. No other comparative evidence in subgroups.

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Appendix A. Glossary

This glossary defines terms as they are used in reports produced by the Drug Effectiveness Review Project. Some definitions may vary slightly from other published definitions.

Absolute risk: The probability or chance that a person will have a medical event. Absolute risk is expressed as a percentage. It is the ratio of the number of people who have a medical event divided by all of the people who could have the event because of their medical condition.

Add-on therapy: An additional treatment used in conjunction with the primary or initial treatment.

Adherence: Following the course of treatment proscribed by a study protocol.

Adverse drug reaction: An adverse effect specifically associated with a drug.

Adverse event: A harmful or undesirable outcome that occurs during or after the use of a drug or intervention but is not necessarily caused by it.

Adverse effect: An **adverse event** for which the causal relation between the intervention and the event is at least a reasonable possibility.

Active-control trial: A trial comparing a drug in a particular class or group with a drug outside of that class or group.

Allocation concealment: The process by which the person determining randomization is blinded to a study participant's group allocation.

Applicability: see *External Validity*

Before-after study: A type nonrandomized study where data are collected before and after patients receive an intervention. Before-after studies can have a single arm or can include a control group.

Bias: A systematic error or deviation in results or inferences from the truth. Several types of bias can appear in published trials, including selection bias, performance bias, detection bias, and reporting bias.

Bioequivalence: Drug products that contain the same compound in the same amount that meet current official standards, that, when administered to the same person in the same dosage regimen result in equivalent concentrations of drug in blood and tissue.

Black box warning: A type of warning that appears on the package insert for prescription drugs that may cause serious adverse effects. It is so named for the black border that usually surrounds the text of the warning. A black box warning means that medical studies indicate that the drug carries a significant risk of serious or even life-threatening adverse effects. The U.S. Food and Drug Administration (FDA) can require a pharmaceutical company to place a black box warning on the labeling of a prescription drug, or in literature describing it. It is the strongest warning that the FDA requires.

Blinding: A way of making sure that the people involved in a research study — participants, clinicians, or researchers —do not know which participants are assigned to each study group. Blinding usually is used in research studies that compare two or more types of treatment for an

illness. Blinding is used to make sure that knowing the type of treatment does not affect a participant's response to the treatment, a health care provider's behavior, or assessment of the treatment effects.

Case series: A study reporting observations on a series of patients receiving the same intervention with no control group.

Case study: A study reporting observations on a single patient.

Case-control study: A study that compares people with a specific disease or outcome of interest (cases) to people from the same population without that disease or outcome (controls).

Clinical diversity: Differences between studies in key characteristics of the participants, interventions or outcome measures.

Clinically significant: A result that is large enough to affect a patient's disease state in a manner that is noticeable to the patient and/or a caregiver.

Cohort study: An observational study in which a defined group of people (the cohort) is followed over time and compared with a group of people who were exposed or not exposed to a particular intervention or other factor of interest. A prospective cohort study assembles participants and follows them into the future. A retrospective cohort study identifies subjects from past records and follows them from the time of those records to the present.

Combination Therapy: The use of two or more therapies and especially drugs to treat a disease or condition.

Confidence interval: The range of values calculated from the data such that there is a level of confidence, or certainty, that it contains the true value. The 95% confidence interval is generally used in Drug Effectiveness Review Project reports. If the report was hypothetically repeated on a collection of 100 random samples of studies, the resulting 100 95% confidence intervals would include the true population value 95% of the time.

Confounder: A factor that is associated with both an intervention and an outcome of interest.

Controlled clinical trial: A clinical trial that includes a control group but no or inadequate methods of randomization.

Control group: In a research study, the group of people who do not receive the treatment being tested. The control group might receive a placebo, a different treatment for the disease, or no treatment at all.

Convenience sample: A group of individuals being studied because they are conveniently accessible in some way. Convenience samples may or may not be representative of a population that would normally be receiving an intervention.

Crossover trial: A type of clinical trial comparing two or more interventions in which the participants, upon completion of the course of one treatment, are switched to another.

Direct analysis: The practice of using data from head-to-head trials to draw conclusions about the comparative effectiveness of drugs within a class or group. Results of direct analysis are the preferred source of data in Drug Effectiveness Review Project reports.

Dosage form: The physical form of a dose of medication, such as a capsule, injection, or liquid. The route of administration is dependent on the dosage form of a given drug. Various dosage

forms may exist for the same compound, since different medical conditions may warrant different routes of administration.

Dose-response relationship: The relationship between the quantity of treatment given and its effect on outcome. In meta-analysis, dose-response relationships can be investigated using meta-regression.

Double-blind: The process of preventing those involved in a trial from knowing to which comparison group a particular participant belongs. While double-blind is a frequently used term in trials, its meaning can vary to include blinding of patients, caregivers, investigators, or other study staff.

Double-dummy: The use of two placebos in a trial that match the active interventions when they vary in appearance or method of administrations (for example, when an oral agent is compared with an injectable agent).

Effectiveness: The extent to which a specific intervention *used under ordinary circumstances* does what it is intended to do.

Effectiveness outcomes: Outcomes that are generally important to patients and caregivers, such as quality of life, responder rates, number and length of hospitalizations, and ability to work. Data on effectiveness outcomes usually comes from longer-term studies of a "real-world" population.

Effect size/estimate of effect: The amount of change in a condition or symptom because of a treatment (compared to not receiving the treatment). It is commonly expressed as a risk ratio (relative risk), odds ratio, or difference in risk.

Efficacy: The extent to which an intervention produces a beneficial result *under ideal conditions* in a selected and controlled population.

Equivalence level: The amount which an outcome from two treatments can differ but still be considered equivalent, as in an equivalence trial, or the amount which an outcome from treatment A can be worse than that of treatment B but still be considered noninferior, as in a noninferiority trial.

Equivalence trial: A trial designed to determine whether the response to two or more treatments differs by an amount that is clinically unimportant. This lack of clinical importance is usually demonstrated by showing that the true treatment difference is likely to lie between a lower and an upper equivalence level of clinically acceptable differences.

Exclusion criteria: The criteria, or standards, set out before a study or review. Exclusion criteria are used to determine whether a person should participate in a research study or whether an individual study should be excluded in a systematic review. Exclusion criteria may include age, previous treatments, and other medical conditions. Criteria help identify suitable participants.

External validity: The extent to which results provide a correct basis for generalizations to other circumstances. For instance, a meta-analysis of trials of elderly patients may not be generalizable to children. (Also called generalizability or applicability.)

Fixed-effect model: A model that calculates a pooled estimate using the assumption that all observed variation between studies is due to by chance. Studies are assumed to be measuring the same overall effect. An alternative model is the random-effects model.

Fixed-dose combination product: A formulation of two or more active ingredients combined in a single dosage form available in certain fixed doses.

Forest plot: A graphical representation of the individual results of each study included in a meta-analysis and the combined result of the meta-analysis. The plot allows viewers to see the heterogeneity among the results of the studies. The results of individual studies are shown as squares centered on each study's point estimate. A horizontal line runs through each square to show each study's confidence interval—usually, but not always, a 95% confidence interval. The overall estimate from the meta-analysis and its confidence interval are represented as a diamond. The center of the diamond is at the pooled point estimate, and its horizontal tips show the confidence interval.

Funnel plot: A graphical display of some measure of study precision plotted against effect size that can be used to investigate whether there is a link between study size and treatment effect.

Generalizability: See *External Validity.*

Half- life: The time it takes for the plasma concentration or the amount of drug in the body to be reduced by 50%.

Harms: See *Adverse Event*

Hazard ratio: The increased risk with which one group is likely to experience an outcome of interest. It is similar to a risk ratio. For example, if the hazard ratio for death for a treatment is 0.5, then treated patients are likely to die at half the rate of untreated patients.

Head-to-head trial: A trial that directly compares one drug in a particular class or group with another in the same class or group.

Health outcome: The result of a particular health care practice or intervention, including the ability to function and feelings of well-being. For individuals with chronic conditions – where cure is not always possible – results include health-related quality of life as well as mortality.

Heterogeneity: The variation in, or diversity of, participants, interventions, and measurement of outcomes across a set of studies.

I^2: A measure of statistical heterogeneity of the estimates of effect from studies. Values range from 0% to 100%. Large values of I^2 suggest heterogeneity. I^2 is the proportion of total variability across studies that is due to heterogeneity and not chance. It is calculated as (Q-(n-1))/Q, where n is the number of studies.

Incidence: The number of new occurrences of something in a population over a particular period of time, e.g. the number of cases of a disease in a country over one year.

Indication: A term describing a valid reason to use a certain test, medication, procedure, or surgery. In the United States, indications for medications are strictly regulated by the Food and Drug Administration, which includes them in the package insert under the phrase "Indications and Usage".

Indirect analysis: The practice of using data from trials comparing one drug in a particular class or group with another drug outside of that class or group or with placebo and attempting to draw conclusions about the comparative effectiveness of drugs within a class or group based on that data. For example, direct comparisons between drugs A and B and between drugs B and C can be used to make an indirect comparison between drugs A and C.

Intention to treat: The use of data from a randomized controlled trial in which data from all randomized patients are accounted for in the final results. Trials often incorrectly report results as being based on intention to treat despite the fact that some patients are excluded from the analysis.

Internal validity: The extent to which the design and conduct of a study are likely to have prevented bias. Generally, the higher the interval validity, the better the quality of the study publication.

Inter-rater reliability: The degree of stability exhibited when a measurement is repeated under identical conditions by different raters.

Intermediate outcome: An outcome not of direct practical importance but believed to reflect outcomes that are important. For example, blood pressure is not directly important to patients but it is often used as an outcome in clinical trials because it is a risk factor for stroke and myocardial infarction (hear attack).

Logistic regression: A form of regression analysis that models an individual's odds of disease or some other outcome as a function of a risk factor or intervention.

Masking: See *Blinding*

Mean difference: A method used to combine measures on continuous scales (such as weight) where the mean, standard deviation, and sample size are known for each group.

Meta-analysis: The use of statistical techniques in a systematic review to integrate the results of included studies. Although the terms are sometimes used interchangeably, meta-analysis is not synonymous with systematic review. However, systematic reviews often include meta-analyses.

Meta-regression: A technique used to explore the relationship between study characteristics (for example, baseline risk, concealment of allocation, timing of the intervention) and study results (the magnitude of effect observed in each study) in a systematic review.

Mixed treatment comparison meta analysis: A meta-analytic technique that simultaneously compares multiple treatments (typical 3 or more) using both direct and indirect evidence. The multiple treatments form a network of treatment comparisons. Also called multiple treatment comparisons, network analysis, or umbrella reviews.

Monotherapy: the use of a single drug to treat a particular disorder or disease.

Multivariate analysis: Measuring the impact of more than one variable at a time while analyzing a set of data.

N-of-1 trial: A randomized trial in an individual to determine the optimum treatment for that individual.

Noninferiority trial: A trial designed to determine whether the effect of a new treatment is not worse than a standard treatment by more than a prespecified amount. A one-sided version of an equivalence trial.

Nonrandomized study: Any study estimating the effectiveness (harm or benefit) of an intervention that does not use randomization to allocate patients to comparison groups. There are many types of nonrandomized studies, including cohort studies, case-control studies, and before-after studies.

Null hypothesis: The statistical hypothesis that one variable (for example, treatment to which a participant was allocated) has no association with another variable or set of variables.

Number needed to harm: The number of people who would need to be treated over a specific period of time before one bad outcome of the treatment will occur. The number needed to harm (NNH) for a treatment can be known only if clinical trials of the treatment have been performed.

Number needed to treat: An estimate of how many persons need to receive a treatment before one person would experience a beneficial outcome.

Observational study: A type of nonrandomized study in which the investigators do not seek to intervene, instead simply observing the course of events.

Odds ratio: The ratio of the odds of an event in one group to the odds of an event in another group. An odds ratio of 1.0 indicates no difference between comparison groups. For undesirable outcomes an odds ratio that is <1.0 indicates that the intervention was effective in reducing the risk of that outcome.

Off-label use: When a drug or device is prescribed outside its specific FDA-approved indication, to treat a condition or disease for which it is not specifically licensed.

Outcome: The result of care and treatment and/ or rehabilitation. In other words, the change in health, functional ability, symptoms or situation of a person, which can be used to measure the effectiveness of care/ treatment/ rehabilitation. Researchers should decide what outcomes to measure before a study begins; outcomes are then assessed at the end of the study.

Outcome measure: Is the way in which an outcome is evaluated---the device (scale) used for measuring. With this definition YMRS is an outcome measure, and a patient's outcome after treatment might be a 12-point improvement on that scale.

One-tailed test (one-sided test): A hypothesis test in which the values that reject the null hypothesis are located entirely in one tail of the probability distribution. For example, testing whether one treatment is better than another (rather than testing whether one treatment is either better or worse than another).

Open-label trial: A clinical trial in which the investigator and participant are aware which intervention is being used for which participant (that is, not blinded). Random allocation may or may not be used in open-label trials.

Per protocol: The subset of participants from a randomized controlled trial who complied with the protocol sufficiently to ensure that their data would be likely to exhibit the effect of treatment. Per protocol analyses are sometimes misidentified in published trials as intention-to-treat analyses.

Pharmacokinetics: the characteristic interactions of a drug and the body in terms of its absorption, distribution, metabolism, and excretion.

Placebo: An inactive substance commonly called a "sugar pill." In a clinical trial, a placebo is designed to look like the drug being tested and is used as a control. It does not contain anything that could harm a person. It is not necessarily true that a placebo has no effect on the person taking it.

Placebo controlled trial: A study in which the effect of a drug is compared with the effect of a placebo (an inactive substance designed to resemble the drug). In placebo controlled clinical

trials, participants receive either the drug being studied or a placebo. The results of the drug and placebo groups are then compared to see if the drug is more effective in treating the condition than the placebo is.

Point estimate: The results (e.g. mean, weighted difference, odds ratio, relative risk or risk difference) obtained in a sample (a study or a meta-analysis) which are used as the best estimate of what is true for the relevant population from which the sample is taken. A confidence interval is a measure of the uncertainty (due to the play of chance) associated with that estimate.

Pooling: The practice of combing data from several studies to draw conclusions about treatment effects.

Power: The probability that a trial will detect statistically significant differences among intervention effects. Studies with small sample sizes can frequently be underpowered to detect difference.

Precision: The likelihood of random errors in the results of a study, meta-analysis, or measurement. The greater the precision, the less the random error. Confidence intervals around the estimate of effect are one way of expressing precision, with a narrower confidence interval meaning more precision.

Prospective study: A study in which participants are identified according to current risk status or exposure and followed forward through time to observe outcome.

Prevalence: How often or how frequently a disease or condition occurs in a group of people. Prevalence is calculated by dividing the number of people who have the disease or condition by the total number of people in the group.

Probability: The likelihood (or chance) that an event will occur. In a clinical research study, it is the number of times a condition or event occurs in a study group divided by the number of people being studied.

Publication bias: A bias caused by only a subset of the relevant data being available. The publication of research can depend on the nature and direction of the study results. Studies in which an intervention is not found to be effective are sometimes not published. Because of this, systematic reviews that fail to include unpublished studies may overestimate the true effect of an intervention. In addition, a published report might present a biased set of results (for example, only outcomes or subgroups for which a statistically significant difference was found).

P value: The probability (ranging from zero to one) that the results observed in a study could have occurred by chance if the null hypothesis was true. A *P* value of ≤ 0.05 is often used as a threshold to indicate statistical significance.

Q-statistic: A measure of statistical heterogeneity of the estimates of effect from studies. Large values of Q suggest heterogeneity. It is calculated as the weighted sum of the squared difference of each estimate from the mean estimate.

Random-effects model: A statistical model in which both within-study sampling error (variance) and between-studies variation are included in the assessment of the uncertainty (confidence interval) of the results of a meta-analysis. When there is heterogeneity among the results of the included studies beyond chance, random-effects models will give wider confidence intervals than fixed-effect models.

Randomization: The process by which study participants are allocated to treatment groups in a trial. Adequate (that is, unbiased) methods of randomization include computer generated schedules and random-numbers tables.

Randomized controlled trial: A trial in which two or more interventions are compared through random allocation of participants.

Regression analysis: A statistical modeling technique used to estimate or predict the influence of one or more independent variables on a dependent variable, for example, the effect of age, sex, or confounding disease on the effectiveness of an intervention.

Relative risk: The ratio of risks in two groups; same as a risk ratio.

Retrospective study: A study in which the outcomes have occurred prior to study entry.

Risk: A way of expressing the chance that something will happen. It is a measure of the association between exposure to something and what happens (the outcome). Risk is the same as probability, but it usually is used to describe the probability of an adverse event. It is the rate of events (such as breast cancer) in the total population of people who could have the event (such as women of a certain age).

Risk difference: The difference in size of risk between two groups.

Risk Factor: A characteristic of a person that affects that person's chance of having a disease. A risk factor may be an inherent trait, such as gender or genetic make-up, or a factor under the person's control, such as using tobacco. A risk factor does not usually cause the disease. It changes a person's chance (or risk) of getting the disease.

Risk ratio: The ratio of risks in two groups. In intervention studies, it is the ratio of the risk in the intervention group to the risk in the control group. A risk ratio of 1 indicates no difference between comparison groups. For undesirable outcomes, a risk ratio that is <1 indicates that the intervention was effective in reducing the risk of that outcome.

Run-in period: Run in period: A period before randomization when participants are monitored but receive no treatment (or they sometimes all receive one of the study treatments, possibly in a blind fashion). The data from this stage of a trial are only occasionally of value but can serve a valuable role in screening out ineligible or non-compliant participants, in ensuring that participants are in a stable condition, and in providing baseline observations. A run-in period is sometimes called a washout period if treatments that participants were using before entering the trial are discontinued.

Safety: Substantive evidence of an absence of harm. This term (or the term ‘‘safe’’) should not be used when evidence on harms is simply absent or is insufficient.

Sample size: The number of people included in a study. In research reports, sample size is usually expressed as "n." In general, studies with larger sample sizes have a broader range of participants. This increases the chance that the study's findings apply to the general population. Larger sample sizes also increase the chance that rare events (such as adverse effects of drugs) will be detected.

Sensitivity analysis: An analysis used to determine how sensitive the results of a study or systematic review are to changes in how it was done. Sensitivity analyses are used to assess how

robust the results are to uncertain decisions or assumptions about the data and the methods that were used.

Side effect: Any unintended effect of an intervention. Side effects are most commonly associated with pharmaceutical products, in which case they are related to the pharmacological properties of the drug at doses normally used for therapeutic purposes in humans.

Standard deviation (SD): A measure of the spread or dispersion of a set of observations, calculated as the average difference from the mean value in the sample.

Standard error (SE): A measure of the variation in the sample statistic over all possible samples of the same size. The standard error decreases as the sample size increases.

Standard treatment: The treatment or procedure that is most commonly used to treat a disease or condition. In clinical trials, new or experimental treatments sometimes are compared to standard treatments to measure whether the new treatment is better.

Statistically significant: A result that is unlikely to have happened by chance.

Study: A research process in which information is recorded for a group of people. The information is known as data. The data are used to answer questions about a health care problem.

Study population: The group of people participating in a clinical research study. The study population often includes people with a particular problem or disease. It may also include people who have no known diseases.

Subgroup analysis: An analysis in which an intervention is evaluated in a defined subset of the participants in a trial, such as all females or adults older than 65 years.

Superiority trial: A trial designed to test whether one intervention is superior to another.

Surrogate outcome: Outcome measures that are not of direct practical importance but are believed to reflect outcomes that are important; for example, blood pressure is not directly important to patients but it is often used as an outcome in clinical trials because it is a risk factor for stroke and heart attacks. Surrogate endpoints are often physiological or biochemical markers that can be relatively quickly and easily measured, and that are taken as being predictive of important clinical outcomes. They are often used when observation of clinical outcomes requires long follow-up.

Survival analysis: Analysis of data that correspond to the time from a well-defined time origin until the occurrence of some particular event or end-point; same as time-to-event analysis.

Systematic review: A review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research and to collect and analyze data from the studies that are included in the review.

Tolerability: For therapeutic drugs, it refers a drug's lack of "nuisance side effects," side effects that are thought to have no long-term effect but that are unpleasant enough to the patient that adherence to the medication regimen is affected.

The extent to which a drug’s adverse effects impact the patient’s ability or willingness to continue taking the drug as prescribed. These adverse effects are often referred to as nuisance side effects, because they are generally considered to not have long-term effects but can seriously impact compliance and adherence to a medication regimen.

Treatment regimen: The magnitude of effect of a treatment versus no treatment or placebo; similar to "effect size". Can be calculated in terms of relative risk (or risk ratio), odds ratio, or risk difference.

Two-tailed test (two-sided test): A hypothesis test in which the values that reject the null hypothesis are located in both tails of the probability distribution. For example, testing whether one treatment is different than another (rather than testing whether one treatment is either better than another).

Type I error: A conclusion that there is evidence that a treatment works, when it actually does not work (false-positive).

Type II error: A conclusion that there is no evidence that a treatment works, when it actually does work (false-negative).

Validity: The degree to which a result (of a measurement or study) is likely to be true and free of bias (systematic errors).

Variable: A measurable attribute that varies over time or between individuals. Variables can be

- *Discrete*: taking values from a finite set of possible values (e.g. race or ethnicity)
- *Ordinal*: taking values from a finite set of possible values where the values indicate rank (e.g. 5-point Likert scale)
- *Continuous:* taking values on a continuum (e.g. hemoglobin A1c values).

Washout period: [In a cross-over trial] The stage after the first treatment is withdrawn, but before the second treatment is started. The washout period aims to allow time for any active effects of the first treatment to wear off before the new one gets started.

Appendix B. Search strategies

Search strategies: Update 4

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <4th Quarter 2005>
Search Strategy:
---
1 (gastroesophageal reflux or gerd).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (1077)
2 (gastrooesophageal reflux or gord).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (87)
3 1 or 2 (1094)
4 (peptic ulcer$ or stomach ulcer$ or gastric ulcer$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (3038)
5 3 or 4 (4097)
6 (pantoprazole or lansoprazole or esomeprazole or omeprazole or rabeprazole).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (2632)
7 (proton pump$ adj3 (antagon$ or inhibit$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (616)
8 6 or 7 (2729)
9 5 and 8 (917)
10 from 9 keep 1-917 (917)

Database: Ovid MEDLINE(R) <1996 to November Week 3 2005>
Search Strategy:
---
1 Gastroesophageal reflux/ or "gerd".mp. (7177)
2 exp peptic ulcer/ or "peptic ulcer".mp. (11820)
3 1 or 2 (18234)
4 Proton pump/ai (2118)
5 proton pump inhibitor$.mp. (2872)
6 (pantoprazole or lansoprazole or esomeprazole or omeprazole or rabeprazole).mp. (4884)
7 4 or 5 or 6 (6850)
8 3 and 7 (3592)
9 limit 8 to (humans and english language) (2806)
10 limit 9 to (clinical trial or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or meta analysis or multicenter study or practice guideline or randomized controlled trial) (947)
11 exp clinical trials/ or clinical trial$.mp. (115736)
12 exp epidemiologic research design/ (288078)
13 observational stud$.mp. (9134)
14 11 or 12 or 13 (394813)
15 9 and 14 (784)
16 10 or 15 (1303)
17 limit 16 to yr="2004 - 2006" (249)
18 from 17 keep 1-249 (249)

Database: Ovid MEDLINE(R) <1996 to November Week 3 2005>
Search Strategy:
---
1 Gastroesophageal reflux/ or "gerd".mp. (7177)
2 exp peptic ulcer/ or "peptic ulcer".mp. (11820)
3 1 or 2 (18234)
4 Proton pump/ai (2118)
5 proton pump inhibitor$.mp. (2872)
6 (pantoprazole or lansoprazole or esomeprazole or omeprazole or rabeprazole).mp. (4884)
7 4 or 5 or 6 (6850)
8 3 and 7 (3592)
9 limit 8 to (humans and english language) (2806)
10 limit 9 to (clinical trial or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or meta analysis or multicenter study or practice guideline or randomized controlled trial) (947)
11 exp clinical trials/ or clinical trial$.mp. (115736)
12 exp epidemiologic research design/ (288078)
13 observational stud$.mp. (9134)
14 11 or 12 or 13 (394813)
15 9 and 14 (784)
16 10 or 15 (1303)
17 limit 16 to yr="2005 - 2006" (107)
18 from 17 keep 1-107 (107)

Database: Ovid MEDLINE(R) <1996 to November Week 3 2005>
Search Strategy:
---
1 Gastroesophageal reflux/ or "gerd".mp. (7177)
2 exp peptic ulcer/ or "peptic ulcer".mp. (11820)
3 1 or 2 (18234)
4 Proton pump/ai (2118)
5 proton pump inhibitor$.mp. (2872)
6 (pantoprazole or lansoprazole or esomeprazole or omeprazole or rabeprazole).mp. (4884)
7 4 or 5 or 6 (6850)
8 3 and 7 (3592)
9 limit 8 to (humans and english language) (2806)
10 limit 9 to (clinical trial or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or meta analysis or multicenter study or practice guideline or randomized controlled trial) (947)
11 exp clinical trials/ or clinical trial$.mp. (115736)
12 exp epidemiologic research design/ (288078)
13 observational stud$.mp. (9134)
14 11 or 12 or 13 (394813)
15 9 and 14 (784)
16 10 or 15 (1303)
17 limit 16 to yr="2003 - 2006" (409)
18 from 17 keep 1-409 (409)

Search strategies: Update 5

Database: Ovid MEDLINE(R) <1996 to September Week 3 2008>

Search Strategy:

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1 Gastroesophageal reflux/ or "gerd".mp. (10132)

2 exp peptic ulcer/ or "peptic ulcer".mp. (14612)

3 1 or 2 (23718)

4 Proton pump/ai (2933)

5 proton pump inhibitor$.mp. (4290)

6 (pantoprazole or lansoprazole or esomeprazole or omeprazole or rabeprazole).mp. (6320)

7 6 or 4 or 5 (9389)

8 3 and 7 (4804)

9 limit 8 to (english language and humans) (3761)

10 limit 9 to (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or controlled clinical trial or meta analysis or multicenter study or practice guideline or randomized controlled trial) (1198)

11 exp clinical trials/ or clinical trial$.mp. (371808)

12 exp epidemiologic research design/ (415174)

13 observational stud$.mp. (15812)

14 11 or 13 or 12 (717226)

15 9 and 14 (1429)

16 10 or 15 (1579)

17 (200511$ or 200512$ or 2006$ or 2007$ or 2008$).ed. (1896250)

18 16 and 17 (338)

19 from 18 keep 1-338 (338)

Database: Ovid MEDLINE(R) <1996 to November Week 2 2008>

Search Strategy:

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1 Gastroesophageal reflux/ or "gerd".mp. (10279)

2 exp peptic ulcer/ or "peptic ulcer".mp. (14721)

3 1 or 2 (23966)

4 Proton pump/ai (2938)

5 proton pump inhibitor$.mp. (4383)

6 (pantoprazole or lansoprazole or esomeprazole or omeprazole or rabeprazole).mp. (6390)

7 6 or 4 or 5 (9527)

8 3 and 7 (4860)

9 limit 8 to (english language and humans) (3807)

10 limit 9 to (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or controlled clinical trial or meta analysis or multicenter study or practice guideline or randomized controlled trial) (1210)

11 exp clinical trials/ or clinical trial$.mp. (375693)

12 exp epidemiologic research design/ (422624)

13 observational stud$.mp. (16191)

14 11 or 13 or 12 (728308)

15 9 and 14 (1444)

16 10 or 15 (1598)

17 (200808$ or 200809$ or 20081$).ed. (201730)

18 16 and 17 (32)

19 from 18 keep 1-32 (32)

Database: Ovid MEDLINE(R) <1996 to March Week 4 2009>

Search Strategy:

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1 Gastroesophageal reflux/ or "gerd".mp. (10634)

2 exp peptic ulcer/ or "peptic ulcer".mp. (15042)

3 1 or 2 (24624)

4 Proton pump/ai (2941)

5 proton pump inhibitor$.mp. (4624)

6 (pantoprazole or lansoprazole or esomeprazole or omeprazole or rabeprazole).mp. (6556)

7 6 or 4 or 5 (9863)

8 3 and 7 (5010)

9 limit 8 to (english language and humans) (3919)

10 limit 9 to (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or controlled clinical trial or meta analysis or multicenter study or practice guideline or randomized controlled trial) (1240)

11 exp clinical trials/ or clinical trial$.mp. (384769)

12 exp epidemiologic research design/ (439367)

13 observational stud$.mp. (17227)

14 11 or 13 or 12 (753726)

15 9 and 14 (1478)

16 10 or 15 (1640)

17 (200811$ or 200812$ or 2009$).ed. (267578)

18 16 and 17 (43)

19 from 18 keep 1-43 (43)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <1st Quarter 2009>

Search Strategy:

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1 (gastroesophageal reflux or gerd).mp. (1361)

2 (gastrooesophageal reflux or gord).mp. (111)

3 1 or 2 (1385)

4 (peptic ulcer$ or stomach ulcer$ or gastric ulcer$).mp. (3261)

5 3 or 4 (4607)

6 (pantoprazole or lansoprazole or esomeprazole or omeprazole or rabeprazole).mp. (3146)

7 (proton pump$ adj3 (antagon$ or inhibit$)).mp. (837)

8 6 or 7 (3296)

9 5 and 8 (1156)

10 limit 9 to yr="2005 -Current" (257)

11 from 10 keep 1-257 (257)

Database: EBM Reviews - Cochrane Database of Systematic Reviews <1st Quarter 2009>

Search Strategy:

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1 (gastroesophageal reflux or gerd).mp. (43)
2 (gastrooesophageal reflux or gord).mp. (17)
3 1 or 2 (49)
4 (peptic ulcer$ or stomach ulcer$ or gastric ulcer$).mp. (103)
5 3 or 4 (145)
6 (pantoprazole or lansoprazole or esomeprazole or omeprazole or rabeprazole).mp. (31)
7 (proton pump$ adj3 (antagon$ or inhibit$)).mp. (42)
8 6 or 7 (51)
9 5 and 8 (35)
10 limit 9 to yr="2005 -Current" (31)
11 from 10 keep 1-31 (31)

Database: EBM Reviews - Database of Abstracts of Reviews of Effects <1st Quarter 2009>
Search Strategy:

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1 (gastroesophageal reflux or gerd).mp. (43)
2 (gastrooesophageal reflux or gord).mp. (5)
3 1 or 2 (43)
4 (peptic ulcer$ or stomach ulcer$ or gastric ulcer$).mp. (77)
5 3 or 4 (113)
6 (pantoprazole or lansoprazole or esomeprazole or omeprazole or rabeprazole).mp. (78)
7 (proton pump$ adj3 (antagon$ or inhibit$)).mp. (86)
8 6 or 7 (110)
9 5 and 8 (68)
10 limit 9 to yr="2005 -Current" [Limit not valid; records were retained] (68)
11 from 10 keep 1-68 (68)

Appendix C. Excluded studies

Exclusion codes
1 = foreign language
2 = wrong outcome
3 = wrong drug
4 = wrong population
5 = wrong publication type
6 = wrong study design

Excluded studies	Exclusion code
Head-to-head trials	
Bigard MA, Genestin E. Treatment of patients with heartburn without endoscopic evaluation: on-demand treatment after effective continuous administration of lansoprazole 15 mg. Alimentary Pharmacology & Therapeutics. Oct 1 2005;22(7):635-643.	6
Castell D, Bagin R, Goldlust B, Major J, Hepburn B. Comparison of the effects of immediate-release omeprazole powder for oral suspension and pantoprazole delayed-release tablets on nocturnal acid breakthrough in patients with symptomatic gastro-esophageal reflux disease. Alimentary pharmacology & therapeutics. Jun 15 2005;21(12):1467-1474.	4
Frazzoni M, De Micheli E, Grisendi A, Savarino V. Effective intra-oesophageal acid suppression in patients with gastro-esophageal reflux disease: lansoprazole vs. pantoprazole. - Alimentary Pharmacology & Therapeutics. 17(2):235-41, 2003 Jan. 2003.	4
Janczewska I, Sagar M, Sjostedt S, Hammarlund B, Iwarzon M, Seensalu R. Comparison of the effect of lansoprazole and omeprazole on intragastric acidity and gastroesophageal reflux in patients with gastroesophageal reflux disease. Scandinavian Journal of Gastroenterology. 1998;33:1239-1243.	4
Johnson M, Guilford S, Libretto SE. Patients have treatment preferences: A multicentre, double-blind, crossover study comparing rabeprazole and omeprazole. Current Medical Research & Opinion. 2002;18(5):303-310.	6
Kumar R, Tandon VR, Bano G, et al. Comparative study of proton pump inhibitors for triple therapy in H. pylori eradication. Indian J Gastroenterol. Mar-Apr 2007;26(2):100-101.	5
Kuwayama H, Luk G, Yoshida S, et al. Efficacy of a low-dose omeprazole-based triple-therapy regimen for Helicobacter pylori eradication independent of cytochrome P450 genotype: The Japanese MACH study. Clinical Drug Investigation. 2005;25(5):293-305.	6
Labenz J, Tillenburg B, Peitz U, et al. Helicobacter pylori augments the pH-increasing effect of omeprazole in patients with duodenal ulcer. Gastroenterology. 1996;110(3):725-732.	2

Lind T, Rydberg L, Kyleback A, et al. Esomeprazole provides improved acid control vs. omeprazole in patients with symptoms of gastro-oesophageal reflux disease. Alimentary Pharmacology & Therapeutics. 2000;14(7):861-867.	4
Miehlke S, Hansky K, Schneider-Brachert W, et al. Randomized trial of rifabutin-based triple therapy and high-dose dual therapy for rescue treatment of Helicobacter pylori resistant to both metronidazole and clarithromycin. Alimentary Pharmacology & Therapeutics. Jul 15 2006;24(2):395-403.	6
Ormeci N, Sarioglu M, Sandikci M, et al. The effectiveness of omeprazole versus lansoprazole along with amoxillicin and clarithromycin in Turkish population with duodenal ulcer. Minerva Gastroenterol Dietol. 2003;49(2):147-153.	1
Regula J, Deckers CPM, Raps D, et al. Comparison of 20 mg and 40 mg Pantoprazole vs 20 mg Omeprazole in the prevention of the development of gastrointestinal lesions in rheumatic patients with continuous NSAID intake. Gut. Nov 2001;49(Suppl 3):1229.	6
Robinson M, Maton PN, Rodriguez S, Greenwood B, Humphries TJ. Effects of oral rabeprazole on oesophageal and gastric pH in patients with gastro-oesophageal reflux disease. Alimentary Pharmacology & Therapeutics. 1997;11(5):973-980.	4
Subei IM, Cardona HJ, Bachelet E, et al. One week of esomeprazole triple therapy vs 1 week of omeprazole triple therapy plus 3 weeks of omeprazole for duodenal ulcer healding in Helicobacter pylori-positive patients. Digestive Diseases & Sciences. Jun 2007;52(6):1505-1512.	6
Tursi A, Brandimarte G, Giorgetti GM, Modeo ME. Effect of Lactobacillus casei supplementation on the effectiveness and tolerability of a new second-line 10-day quadruple therapy after failure of a first attempt to cure Helicobacter pylori infection. Medical science monitor : international medical journal of experimental and clinical research. 2004;10(12):CR662-666.	6
Vakil NB, Traxler B, Levine D. Dysphagia in patients with erosive esophagitis: prevalence, severity, and response to proton pump inhibitor treatment. Clinical Gastroenterology & Hepatology. Aug 2004;2(8):665-668.	6
Wong BC, Wang WH, Wong WM, et al. Three-day lansoprazole quadruple therapy for Helicobacter pylori-positive duodenal ulcers: a randomized controlled study. Alimentary Pharmacology & Therapeutics. 2001;15(6):843-849.	6
Active-control trials	
Lansoprazole versus ranitidine in the treatment of reflux esophagitis. Multicentric study. Med Chir Dig. 1991;20(8):462-468."	1
Adachi K, Hashimoto T, Komazawa Y, et al. Helicobacter pylori infection influences symptomatic response to anti-secretory therapy in patients with GORD--crossover comparative study with famotidine and low-dose lansoprazole. Digestive & Liver Disease. Jul 2005;37(7):485-490.	6

Arkkila PE, Seppala K, Kosunen TU, et al. Helicobacter pylori eradication as the sole treatment for gastric and duodenal ulcers. European journal of gastroenterology & hepatology. 2005;17(1):93-101.	6
Awad RA, Camacho S, Dibildox M. Pantoprazole effectively controls intra-oesophageal pH and promotes oesophageal healing: Further evidence for ranitidine-induced tolerance in patients with gastro-oesophageal reflux disease. Clinical Drug Investigation. 2001;21(4):265-272.	6
Bardham KD, Muller-Lissner S, Bigard MA, et al. Symptomatic gastro-oesophageal reflux disease: Double blind controlled study of intermittent treatment with omeprazole or ranitidine. BMJ. 1999;British Medical Journal. 318(7182):502-507.	6
Bate CM, Green JR, Axon AT, et al. Omeprazole is more effective than cimetidine for the relief of all grades of gastro-oesophageal reflux disease-associated heartburn, irrespective of the presence or absence of endoscopic oesophagitis. Alimentary pharmacology & therapeutics. 1997;11(4):755-763.	6
Bigard MA, Isal JP, Galmiche JP, Ebrard F, Bader JP. Omeprazole versus cimetidine in short-term treatment of acute duodenal ulcer. Gastroenterol-Clin-Biol, Issn:. 1987;0399-8320. 11(11):753-757.	1
Bochenek WJ, Mack ME, Fraga PD, Metz DC. Pantoprazole provides rapid and sustained symptomatic relief in patients treated for erosive oesophagitis. Alimentary pharmacology & therapeutics. 2004;20(10):1105-1114.	6
Buzas GM, Gyorffy H, Szeles I, Szentmihalyi A. Second-line and third-line trial for helicobacter pylori infection in patients with duodenal ulcers: A prospective, crossover, controlled study. Current Therapeutic Research - Clinical and Experimental. 2004;65(1):13-25.	6
Cataldo MG, Brancato D, Donatelli M, Morici ML, Aspetti S, Spina P. Treatment of patients with duodenal ulcer positive for Helicobacter pylori infection: Ranitidine or omeprazole associated with colloidal bismuth subcitrate plus amoxicillin. Current Therapeutic Research Clinical and Experimental. 1996;57(3):168-174.	6
Cisternino M. Omeprazole 20 mg uid and ranitidine 150 mg bid in the treatment of benign gastric ulcer. Italian Cooperative Group on Omeprazole. Hepato-Gastroenterology. 1991;38(5):400-403.	6
Classen M, Dammann HG, Domschke W, et al. Short-duration treatment of duodenal ulcer with omeprazole and ranitidine: Results of a multi-centre trial in Germany. Dtsch-Med-Wochenschr. 1985;110(6):210-215.	1
Cucchiara S, Minella R, Iervolino C, et al. Omeprazole and high dose ranitidine in the treatment of refractory reflux oesophagitis. Archives of Disease in Childhood. 1993;69(6):655-659.	6
Dickman R, Schiff E, Holland A, et al. Clinical trial: acupuncture vs. doubling the proton pump inhibitor dose in refractory heartburn. Alimentary Pharmacology & Therapeutics. Nov 15 2007;26(10):1333-1344.	6

Figura N, Minoli G, Fedeli G, Cammarota G, Mazzilli D, Bayeli PF. Omeprazole versus ranitidine in the prevention of duodenal ulcer recurrence after eradication therapy. Current Therapeutic Research Clinical and Experimental. 1995;56(6):568-572.	6
Fujiwara Y, Higuchi K, Nebiki H, et al. Famotidine vs. omeprazole: a prospective randomized multicentre trial to determine efficacy in non-erosive gastro-oesophageal reflux disease. Alimentary pharmacology & therapeutics. Jun 2005;21 Suppl 2:10-18.	6
Hotz J, Kark W, Plein K, Wiedbrauck F, Guthke A, Otten O. Management of acute gastroduodenal peptic ulcer: Superiority of omeprazole to ranitidine in the early phase of ulcer healing. Leber Magen Darm. 1995;25(4):165-170.	1
Howden CW, Henning JM, Huang B, Lukasik N, Freston JW. Management of heartburn in a large, randomized, community-based study: comparison of four therapeutic strategies. American Journal of Gastroenterology. 2001;96(6):1704-1710.	6
Hsu PI, Lo GH, Lo CC, et al. Intravenous pantoprazole versus ranitidine for prevention of rebleeding after endoscopic hemostasis of bleeding peptic ulcers. World journal of gastroenterology : WJG. 2004;10(24):3666-3669.	3
Hu FL, Jia JC, Li YL, Yang GB. Comparison of H2-receptor antagonist- and proton-pump inhibitor-based triple regimens for the eradication of Helicobacter pylori in Chinese patients with gastritis or peptic ulcer. Journal of International Medical Research. 2003;31(6):469-474.	6
Hungin APS, Gunn SD, Bate CM, Turbitt ML, Wilcock C, Richardson PDI. A comparison of the efficacy of omeprazole 20 mg once daily with ranitidine 150 mg bd in the relief of symptomatic gastro-oesophageal reflux disease in general practice. British Journal of Clinical Research. 1993;4:73-88.	6
Itoh M, Matsuo Y, Choi KW, et al. Gastric ulcer treatment with intravenous human epidermal growth factor: a double-blind controlled clinical study.: A double-blind, randomized, parallel group study of omeprazole and ranitidine in Korean patients with gastric ulcer. J Gastroenterol Hepatol. 1994;9 Suppl 1(2):S78-83-118-123.	3
Jiang M, Chen ZM, Tsukahara H, et al. Relationship between gastric acid suppression and healing of peptic ulcers in children. International Medical Journal. 2001;8(3):199-203.	1
Kato S, Ritsuno H, Ohnuma K, Iinuma K, Sugiyama T, Asaka M. Safety and efficacy of one-week triple therapy for eradicating Helicobacter pylori in children. Helicobacter. 1998;3(4):278-282.	6
Kato S, Takeyama J, Ebina K, Naganuma H. Omeprazole-based dual and triple regimens for Helicobacter pylori eradication in children. Pediatrics. 1997;100(1):E3.	6

Kovacs TO, Wilcox CM, DeVault K, Miska D, Bochenek W, Pantoprozole USGSGB. Comparison of the efficacy of pantoprazole vs. nizatidine in the treatment of erosive oesophagitis: a randomized, active-controlled, double-blind study. Alimentary pharmacology & therapeutics. 2002;16(12):2043-2052.	6
Kuipers EJ, Nelis GF, Klinkenberg-Knol EC, et al. Cure of Helicobacter pylori infection in patients with reflux oesophagitis treated with long term omeprazole reverses gastritis without exacerbation of reflux disease: results of a randomised controlled trial. Gut. 2004;53(1):12-20.	6
Lewin-Van Den Broek NT, Numans ME, Buskens E, Verheij TJM, De Wit NJ, Smout A. A randomised controlled trial of four management strategies for dyspepsia: Relationships between symptom subgroups and strategy outcome. British Journal of General Practice. 2001;51(469):619-624.	6
Lin CK, Lai KH, Lo GH, et al. Efficacy of omeprazole versus famotidine in the short-term treatment of gastric ulcer. Chinese Journal of Gastroenterology. 1995;11(4):13-17.	1
Lundell L, Attwood S, Ell C, et al. Comparing laparoscopic antireflux surgery with esomeprazole in the management of patients with chronic gastro-oesophageal reflux disease: a 3-year interim analysis of the LOTUS trial. Gut. Sep 2008;57(9):1207-1213.	6
Mahon D, Rhodes M, Decadt B, et al. Randomized clinical trial of laparoscopic Nissen fundoplication compared with proton-pump inhibitors for treatment of chronic gastro-oesophageal reflux. The British journal of surgery. 2005;92(6):695-699.	5
Malfertheiner P, Dent J, Zeijlon L, et al. Impact of Helicobacter pylori eradication on heartburn in patients with gastric or duodenal ulcer disease - Results from a randomized trial programme. Alimentary Pharmacology & Therapeutics. 2002;16(8):1431-1442.	6
Michel P, Lemaire M, Colin R, et al. Short report: treatment of gastric ulcer with lansoprazole or ranitidine: a multicentre clinical trial. Alimentary pharmacology & therapeutics. 1994;8(1):119-122.	6
Miyake K, Ueki N, Suzuki K, et al. Preventive therapy for non-steroidal anti-inflammatory drug-induced ulcers in Japanese patients with rheumatoid arthritis: the current situation and a prospective controlled-study of the preventive effects of lansoprazole or famotidine. Alimentary pharmacology & therapeutics. Jun 2005;21 Suppl 2:67-72.	3
Okada M, Oki K, Shirotani T, et al. A new quadruple therapy for the eradication of Helicobacter pylori. Effect of pretreatment with omeprazole on the cure rate. Journal of Gastroenterology. 1998;33(5):640-645.	6
Pare P, Bailey RJ, Archambault AP, et al. Healing of benign gastric and prepyloric ulcers: A prospective, endoscopy-controlled, randomized, double-blind, Canadian multicentre study of omeprazole 20 and 40 mg daily and ranitidine 150 mg twice a day. Can J Gastroenterol. 1990;4(1):7-12.	6

Pilotto A, Di Mario F, Franceschi M, et al. Pantoprazole versus one week Helicobacter pylori eradication therapy for the prevention of acute NSAID related gastroduodenal damage in elderly subjects. Alimentary Pharmacology & Therapeutics. 2000;14:1077-1082.	6
Popovic O, Dzambas D, Tasic T, Bidikov V, Jesenski T, Janosevic S. Omeprazole 20 mg o.m. vs. famotidine 40 mg h.s. in the treatment of duodenal ulcer. Multicenter double-blind randomized trial. Gastroenterohepatoloski Arh. 1990;9(1):26-34.	1
Puig LG, Santaella RA, Aparicio PG, et al. Healing of gastric or pre-pyloric ulcers with once daily omeprazole 20 mg or ranitidine 300 mg. Journal of Drug Development and Clinical Practice. 1995;7(3):173-180.	6
Richter JE, Campbell DR, Kahrilas PJ, Huang B, Fludas C. Lansoprazole compared with ranitidine for the treatment of nonerosive gastroesophageal reflux disease. Archives of Internal Medicine. 2000;160:1803-1809.	6
Russo A, Dattilo M. Bedtime administration of lansoprazole does not modify its greater efficacy vs ranitidine in the acute and long term treatment of duodenal ulcer. Results from a multicentre, randomised, double blind clinical trial. Italian Journal of Gastroenterology & Hepatology. 1997;29:312-319.	6
Shi L, Zhu LY, Shi S, Shun GX. Contrastive Study of Effect of Lansoprazole and Ranitidine On Treatment in Gastric Ulcer Disease. Journal of Henan Medical Staff College. 2000;12(3):18-19.	1
Si J-M, Cao Q, Wu J-G. Quality of gastric ulcer healing evaluated by endoscopic ultrasonography. World Journal of Gastroenterology. Jun 14 2005;11(22):3461-3464.	3
Wada T, Sasaki M, Kataoka H, et al. Efficacy of famotidine and omeprazole in healing symptoms of non-erosive gastro-oesophageal reflux disease: randomized-controlled study of gastro-oesophageal reflux disease. Alimentary pharmacology & therapeutics. Jun 2005;21 Suppl 2:2-9.	6
Yang PJ, Chen RC, Wang TH. Eradication of Helicobacter pylori with omeprazole-amoxicillin combination therapy versus famotidine. A randomized, controlled study. Gastroenterological Journal of Taiwan. 1996;13(1):13-20.	2
Yeomans N, Wilson I, Langstrom G, et al. Quality of life in chronic NSAID users: a comparison of the effect of omeprazole and misoprostol. Scandinavian journal of rheumatology. 2001;30(6):328-334.	6
Placebo-controlled trials	
Avner DL, Dorsch ER, Jennings DE, Greski RPA. A comparison of three doses of lansoprazole (15, 30 and 60 mg) and placebo in the treatment of duodenal ulcer. Aliment Pharmacol Ther. 1995;9(5):521-528.	6
Bochenek WJ, Peters S, Fraga PD, et al. Eradication of Helicobacter pylori by 7-day triple-therapy regimens combining pantoprazole with clarithromycin, metronidazole, or amoxicillin in patients with peptic ulcer disease: results of two double-blind, randomized studies. Helicobacter. 2003;8(6):626-642.	6

Feng LY, Yao XX, Jiang SL. Effects of killing Helicobacter pylori quadruple therapy on peptic ulcer: a randomized double-blind clinical trial. World journal of gastroenterology : WJG. 2005;11(7):1083-1086.	6
Giral A, Ozdogan O, Celikel CA, Tozun N, Ulusoy NB, Kalayci C. Effect of Helicobacter pylori eradication on anti-thrombotic dose aspirin-induced gastroduodenal mucosal injury. J Gastroenterol Hepatol. 2004;19(7):773-777.	4
Gold BD. A randomized, double-blind, placebo-controlled study of gastroesophageal reflux disease therapy. ClinicalTrials.gov. 2005.	4
Hawkey C, Talley NJ, Yeomans ND, et al. Improvements with esomeprazole in patients with upper gastrointestinal symptoms taking non-steroidal antiinflammatory drugs, including selective COX-2 inhibitors. The American journal of gastroenterology. 2005;100(5):1028-1036.	2
Johnson DA, Orr WC, Crawley JA, et al. Effect of esomeprazole on nighttime heartburn and sleep quality in patients with GERD: a randomized, placebo-controlled trial. American Journal of Gastroenterology. Sep 2005;100(9):1914-1922.	6
Juul-Hansen P, Rydning A, Ditlef Jacobsen C, Hansen T. High-dose proton-pump inhibitors as a diagnostic test of gastro-oesophageal reflux disease in endoscopic-negative patients. Scandinavian Journal of Gastroenterology. 2001;36(8):806-810.	4
Lundell L. New information relevant to long-term management of endoscopy-negative reflux disease. Alimentary Pharmacology and Therapeutics, Supplement. 1997;11(2):93-98.	5
Richter JE, Kovacs TO, Greski-Rose PA, Huang B, Fisher R. Lansoprazole in the treatment of heartburn in patients without erosive oesophagitis. Alimentary Pharmacology & Therapeutics. 1999;13:795-804.	6
Richter JE, Peura D, Benjamin SB, Joelsson B, Whipple J. Efficacy of omeprazole for the treatment of symptomatic acid reflux disease without esophagitis. Archives of Internal Medicine. 2000;160:1810-1816.	6
Scholten T, Dekkers CPM, Schutze K, Korner T, Bohuschke M, Gatz G. On-demand therapy with pantoprazole 20 mg as effective long-term management of reflux disease in patients with mild GERD: the ORION trial. Digestion. 2005;72(2-3):76-85.	6
Wheeldon TU, Granstrom M, Hoang TT, Phuncarg DC, Nilsson LE, Sorberg M. The importance of the level of metronidazole resistance for the success of Helicobacter pylori eradication. Alimentary Pharmacology & Therapeutics. 2004;19(12):1315-1321.	6
Williams MP, Sercombe J, Hamilton MI, Pounder RE. A placebo-controlled trial to assess the effects of 8 days of dosing with rabeprazole versus omeprazole on 24-h intragastric acidity and plasma gastrin concentrations in young healthy male subjects. Alimentary Pharmacology & Therapeutics. 1998;12:1079-1089.	4
Yi C-H, Chen C-L, Kuo TBJ, Yang CCH. The effect of acid suppression on sleep and cardiac autonomic regulation in GERD. Hepato-Gastroenterology. Sep-Oct 2008;55(86-87):1649-1652.	4

Appendix D. Quality assessment methods for drug class reviews for the Drug Effectiveness Review Project

Study quality is objectively assessed using predetermined criteria for internal validity, based on the combination of the US Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination criteria. This appendix lists questions that are posed for each included study in order to assess study quality. These quality-assessment questions differ for systematic reviews, controlled trials, and nonrandomized trials.

Regardless of design, all studies that are included are assessed for quality and assigned a rating of "good," "fair," or "poor." Studies with fatal flaws are rated poor quality. A fatal flaw is failure to meet combinations of criteria that may indicate the presence of bias. An example would be inadequate procedure for randomization or allocation concealment combined with important differences in prognostic factors at baseline. Studies that meet all criteria are rated good quality, and the remainder is rated fair quality. As the fair-quality category is broad, studies with this rating vary in their strengths and weaknesses: The results of some fair-quality studies are likely to be valid, while others are only probably valid. A poor-quality trial is not valid; the results are at least as likely to reflect flaws in the study design as a true difference between the compared drugs.

Systematic Reviews

1. Does the review report a clear review question and inclusion/exclusion criteria that relate to the primary studies?
   A good-quality review should focus on a well-defined question or set of questions. These questions ideally are reflected in the inclusion/exclusion criteria, which guide the decision of whether to include or exclude specific primary studies. The criteria should relate to the 4 components of study design: indications (patient populations), interventions (drugs), and outcomes of interest. In addition, details should be reported relating to the process of decision-making, such as how many reviewers were involved, whether the studies were examined independently, and how disagreements between reviewers were resolved.

2. Is there evidence of a substantial effort to search for all relevant research?
   If details of electronic database searches and other identification strategies are given, the answer to this question usually is yes. Ideally, search terms, dates, and language restrictions should be presented. In addition, descriptions of hand searching, attempts to identify unpublished material, and any contact with authors, industry, and research institutes should be provided. The appropriateness of the database(s) searched by the authors should also be considered. For example, if only Medline was searched for a review looking at proton pump inhibitors then it is unlikely that all relevant studies were located.

3. Is the validity of included studies adequately assessed?
   A systematic assessment of the quality of primary studies should include an explanation of the criteria used (for example, how randomization was done, whether outcome

assessment was blinded, whether analysis was on an intention-to-treat basis). Authors may use a published checklist or scale or one that they have designed specifically for their review. Again, the process relating to the assessment should be explained (how many reviewers were involved, whether the assessment was independent, and how discrepancies between reviewers were resolved).

4. Is sufficient detail of the individual studies presented?
   The review should demonstrate that the studies included are suitable to answer the question posed and that a judgment on the appropriateness of the authors' conclusions can be made. If a paper includes a table giving information on the design and results of the individual studies or includes a narrative description of the studies within the text, this criterion is usually fulfilled. If relevant, the tables or text should include information on study design, sample sizes, patient characteristics, interventions, settings, outcome measures, follow-up periods, drop-out rates (withdrawals), effectiveness results, and adverse events.

5. Are the primary studies summarized appropriately?
   The authors should attempt to synthesize the results from individual studies. In all cases, there should be a narrative summary of results, which may or may not be accompanied by a quantitative summary (meta-analysis). For reviews that provide a meta-analysis, heterogeneity between studies should be assessed using statistical techniques. If heterogeneity is present, the possible reasons (including chance) should be investigated. In addition, the individual studies should be weighted in some way (for example, according to sample size or inverse of the variance) so that studies that are considered to provide the most reliable data have greater impact on the summary statistic.

Controlled Trials

Assessment of internal validity

1. Was the assignment to treatment groups really random?
   Adequate approaches to sequence generation:
   - Computer-generated random numbers
   - Random-numbers table

   Inferior approaches to sequence generation:
   - Use of alternation, case record number, birth date, or day of week

   Not reported

2. Was the treatment allocation concealed?
   Adequate approaches to concealment of randomization:
   - Centralized or pharmacy-controlled randomization
   - Serially numbered identical containers
   - On-site computer-based system with a randomization sequence that is not readable until allocation

   Inferior approaches to concealment of randomization:
   - Use of alternation, case record number, birth date, or day of week

Open random-numbers list
Serially numbered envelopes (Even sealed opaque envelopes can be subject to manipulation.)
Not reported

3. Were the groups similar at baseline in terms of prognostic factors?

4. Were the eligibility criteria specified?

5. Were outcome assessors blinded to the treatment allocation?

6. Was the care provider blinded?

7. Was the patient kept unaware of the treatment received?

8. Did the article include an intention-to-treat analysis or provide the data needed to calculate it (number assigned to each group, number of subjects who finished in each group, and their results)?

9. Did the study maintain comparable groups?

10. Did the article report attrition, crossovers, adherence, and contamination?

11. Is there important differential loss to followup or overall high loss to followup (giving numbers for each group)?

Assessment of external validity (applicability)

1. How similar is the population to the population to which the intervention would be applied?

2. How many patients were recruited?

3. What were the exclusion criteria for recruitment? (Give numbers excluded at each step.)

4. What was the funding source and role of funder in the study?

5. Did the control group receive the standard of care?

6. What was the length of follow-up? (Give numbers at each stage of attrition.

Nonrandomized Studies

Assessment of internal validity

1. Was the selection of patients for inclusion unbiased? In other words, was any group of patients systematically excluded?

2. Is there important differential loss to follow-up or overall high loss to follow-up? (Give numbers in each group.)

3. Were the investigated events specified and defined?

4. Was there a clear description of the techniques used to identify the events?

5. Was there unbiased and accurate ascertainment of events (independent ascertainers and validation of ascertainment technique)?

6. Were potential confounding variables and risk factors identified and examined using acceptable statistical techniques?

7. Did the duration of follow-up correlate with reasonable timing for investigated events? (Does it meet the stated threshold?)

Assessment of external validity

1. Was the description of the population adequate?

2. How similar is the population to the population to which the intervention would be applied?

3. How many patients were recruited?

4. What were the exclusion criteria for recruitment? (Give numbers excluded at each step.)

5. What was the funding source and role of funder in the study?

References:

Centre for Reviews and Dissemination. *Undertaking systematic reviews of research on effectiveness: CRD's guidance for those carrying out or commissioning reviews.* CRD Report Number 4. 2nd ed. University of York, UK; 2001.

Harris RP, Helfand M, Woolf SH, et al. Current methods of the US Preventive Services Task Force: a review of the process. *Am J Prev Med.* Apr 2001;20(3 Suppl):21-35.

Appendix E. Esophagitis grading scales used in randomized controlled trials

Savary-Miller

Grade I: one or more supravestibular, non-confluent reddish spots, with or without exudate.

Grade II: erosive and exudative lesions in the distal esophagus which may be confluent, but not

Grade III: circumferential erosions in the distal esophagus, covered by hemorrhagic and pseudomembranous exudates.

Grade IV: presence of chronic complications such as deep ulcers, stenosis, or scarring with Barrett's metaplasia.

Modified Hetzel-Dent

Grade 0: Normal mucosa, no abnormalities found

Grade 1: No macroscopic erosions, but presence of erythema, hyperemia, and/or friability of the esophageal mucosa.

Grade 2: Superficial ulceration or erosions involving less than 10% of the mucosal surface area of the last 5 cm of esophageal squamous mucosa.

Grade 3: Superficial ulceration or erosions involving greater than or equal to 10% but less than 50% of the mucosal surface area of the last 5 cm of esophageal squamous mucosa.

Grade 4: Deep ulceraton anywhere in the esophagus or confluent erosion of more than 50% of the mucosal surface area of the last 5 cm of esophageal squamous mucosa.

Grade 5: Stricture, defined as a narrowing of the esophagus that does not allow easy passage of the endoscope without dilation.

Los Angeles Classification

Not present: No breaks (erosions) in the esophageal mucosa (edema, erythema, or friability may be present)

Grade A: One or more mucosal breaks confined to the mucosal folds, each not more than 5 mm in maximum length.

Grade B: One or more mucosal breaks more than 5 mm in maximum length, but not continuous between the tops of two mucosal folds.

Grade C: Mucosal breaks that are continuous between the tops of tow or more mucosal folds, but which involve less that 75% of the esophageal circumference.

Grade D: Mucosal breaks which involve at least 75% of the esophageal circumference.

The presence or absence of strictures, ulcers, and/or Barrett's esophagus much be noted separately, e.g., "Grade B with stricture".

Criteria used in Hatlebakk, 1993:

Grade 1: red streaks or spots along the ridge of the folds in the distal esophagus, covered or not by fibrinous Exudate

Grade 2: Broader lesions, each involving the entire width of a fold or coalescing into fields or erythema, covered or not with fibrinous exudates

Grade 3: Stricture or endoscopically visible ulcer in distal esophagus.

Criteria used in Castell, 1996, Howden, 2002, Richter 2001b:

Grade 0: normal-appearing mucosa

Grade 1: mucosal edema, hyperemia, and/or friability

Grade 2: one or more erosions/ulcerations involving <10% of the distal 5 cm of the esophagus

Grade 3: erosions/ulcerations involving 10-50% of the distal 5 cm of the esophagus or an ulcer 3-5 mm in diameter. In cases of Barrett's esophagus, the area 5 cm proximal to the squamocolumnar junction was evaluated

Grade 4: multiple erosions involving >50% of the distal 5 cm of the esophagus or a single ulcer > 5mm in diameter.

Drug Class Review

Proton Pump Inhibitors

Final Report Update 5
Evidence Tables

April 2009

Update 4: May 2006
Update 3: May 2005
Update 2: April 2004
Update 1: April 2003
Original Report: November 2002

The literature on this topic is scanned periodically.

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use, or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

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The medical literature relating to this topic is scanned periodically. (See http://www.ohsu.edu/ohsuedu/research/policycenter/DERP/about/methods.cfm for description of scanning process). Prior versions of this report can be accessed at the DERP website.

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Population, Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks
Adachi et al, 2003	85 patients at 6 medical institutions in Japan. Mean age 66 (SD 13); 51% male; 100% Asian	Grade A: 24% Grade B: 53% Grade C: 21% Grade D: 2% (Los Angeles classification) 42% h. Pylori positive	Screened NR/eligible NR/85 enrolled 20% of lansoprazole group lost to f/u for endoscopy vs 7% in other groups; but no loss to f/u for reporting of symptoms 85 analyzed for symptoms, 76 for endoscopy	Not reported

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Healing Rate at 8 Weeks	Symptoms at 4 Weeks	Symptoms at 8 Weeks
Adachi et al, 2003	(Per protocol analysis on 76 patients): omeprazole 20 mg: 85.7% lansoprazole 30 mg: 85% rabeprazole 20 mg: 92.9% (NS)	(Results reported graphically only) Heartburn score significantly lower in rabeprazole group after 2 days than lansoprazole or omeprazole (p=0.045). Differences disappeared by day 5. No significant differences in acid reflux scores.	Not reported

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Results by Baseline Severity	Withdrawals Due to Adverse Events	Quality rating	Funding source
Adachi et al, 2003	Not reported	Not reported	Fair: open-label, loss to f/u higher in lansoprazole group for healing (20% vs 7%), but okay for symptoms; randomization method not reported	Ministry of Education, Science, and Culture of Japan

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Population, Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks
Bardhan et al, 2001	328 patients at 23 centers in Great Britain, the Republic of Ireland, and South Africa. Mean age 44.6 (SD 13.3) in pantoprazole group, 45.2 (SD14.4) in omeprazole group. 52.4% of pantoprazole, 64% of omeprazole group males. Race/ethnicity not reported.	100% Grade I (Savary-Miller classification)	Screened NR/eligible NR/328 enrolled/ 327 analyzed	Intention-to-treat (N=327): pantoprazole 20 mg: 77% omeprazole 20 mg: 81% Per-protocol (N=264): pantoprazole 20 mg: 84% omeprazole 20 mg: 89%

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Healing Rate at 8 Weeks	Symptoms at 4 Weeks	Symptoms at 8 Weeks
Bardhan et al, 2001	Intention-to-treat (N=327): pantoprazole 20 mg: 81% omeprazole 20 mg: 88% (NS) Per-protocol (N=264): pantoprazole 20 mg: 90% omeprazole 20 mg: 95% (NS)	pantoprazole 20 mg vs omeprazole 20 mg Symptom relief (all main symptoms) 2 weeks: 70% vs 79% 4 weeks: 77% vs 84% Acid eructation 2 weeks: 79% vs 88% 4 weeks: 84% vs 87% Heartburn 2 weeks: 79% vs 86% 4 weeks: 83% vs 87% Pain on swallowing 2 weeks: 83% vs 87% 4 weeks: 87% vs 97% (All NS)	Not reported

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Results by Baseline Severity	Withdrawals Due to Adverse Events	Quality rating	Funding source
Bardhan et al, 2001	Relief of acid eructation, heartburn and pain on swallowing was similar in the two treatment groups at 2 and 4 weeks, irrespective of severity at baseline. A higher proportion with mild symptoms at entry had relief compared with patients with severe symptoms, and this was similar for both treatments.	Not reported	Fair-Poor: open-label, randomization, allocation concealment method not reported, more smokers in pantoprazole group (31% vs 22%), more males in omeprazole group (64% vs 52%)	Byk Gulden (Germany) pharmaceutical

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Population, Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks
Chen et al, 2005	48 patients at a single center in Taiwan. Mean age 53.9 79.2% male Race NR	Grade A: 54.2% Grade B: 29.2% Grade C: 8.3% Grade D: 8.3% (Los Angeles classification)	Screened, eligible NR/48 enrolled 2 withdrawn/2 lost to followup/42 analyzed per protocol, 47 analyzed ITT	esomeprazole 40 mg: NR omeprazole 20 mg: NR

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Healing Rate at 8 Weeks	Symptoms at 4 Weeks	Symptoms at 8 Weeks
Chen et al, 2005	PP patients (n=42) esomeprazole 40 mg: 72.7% omeprazole 20 mg: 50% ITT patients (n=47) esomeprazole 40 mg: 64% omeprazole: 20 mg: 45.5% OR 2.667 (PP: 95% CI 0.739-9.63, P=0.2040)	NR	*Heartburn:* esomeprazole 40 mg: 50% improved, 50% no change omeprazole 20 mg: 65% improved, 25% no change, 10% worse (p=0.0993) *Regurgitation:* esomeprazole 40 mg: 77.3% improved, 18.2% no change, 4.5% worse omeprazole 20 mg: 85.0% improved, 15.0% no change (p=1.0000) *Dysphagia:* esomeprazole 40 mg: 36.4% improved, 63.6% no change omeprazole 20 mg: 35.0% improved, 60.0% no change, 5.0% worse (p=0.8697) *Epigastric pain:* esomeprazole 40 mg: 27.3% improved, 63.6% no change, 9.1% worse omeprazole 20 mg: 50.0% improved, 50.0% no change (p=0.1895) *Nausea:* esomeprazole 40 mg: 22.7% improved, 68.2% no change, 9.1% worse omeprazole 20 mg: 35.0% improved, 65.0% no change (p=0.5036) *Vomiting:* esomeprazole 40 mg: 22.7% improved, 77.3% no change omeprazole 20 mg: 40.0% improved, 60.0% no change (p=0.3200) *Belching:* esomeprazole 40 mg: 54.5%, 36.4% no change, 9.1% worse omeprazole 20 mg: 45.0% improved, 45.0% no change, 10.0% worse (p=0.8999)

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Results by Baseline Severity	Withdrawals Due to Adverse Events	Quality rating	Funding source
Chen et al, 2005	Not quantitatively expressed, see Figure 1. Difference stated as not SS different.	NR	Fair	NR (AstraZeneca provided randomization schedule)

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Population, Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks
Fennerty, 2005	999 patients at multiple centers in the US, with moderate to severe esophagitis. Mean age 47 66% male 82% white, 5% black, <1% Asian, 13% other	Grade C: 79% Grade D: 21% (Los Angeles classification)	4015 screened/ 1381 eligible/ 1001 enrolled/ 11 withdrew/ 18 lost to followup/ 999 analyzed	esomeprazole 40 mg: 55.8% lansoprazole 30 mg: 47.5% (p<0.005)

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Healing Rate at 8 Weeks	Symptoms at 4 Weeks	Symptoms at 8 Weeks
Fennerty, 2005	esomeprazole 40 mg: 77.5% lansoprazole 30 mg: 73.3% (p=0.099)	*Resolution of heartburn:* esomeprazole 40 mg: 72% lansoprazole 30 mg: 63.6% (p=0.005) *Resolution of acid regurgitation:* esomeprazole 40 mg: 79.5% lansoprazole 30 mg: 76.2% (p=0.203) *Dysphagia:* esomeprazole 40 mg: 93.1% lansoprazole 30 mg: 93.8% (p=0.614) *Epigastric pain:* esomeprazole 40 mg: 83.1% lansoprazole 30 mg: 82.6% (p=0.831)	Not reported

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Results by Baseline Severity	Withdrawals Due to Adverse Events	Quality rating	Funding source
Fennerty, 2005	Grade C *Healing at 4 weeks* esomeprazole 40 mg: 60.3% lansoprazole 30 mg: 50.6% (p-value not reported) *Healing at 8 weeks* esomeprazole 40 mg: 80.3% lansoprazole 30 mg: 74.9% (p-value not reported) Grade D *Healing at 4 weeks* esomeprazole 40 mg: 39.8% lansoprazole 30 mg: 34.7% (p-value not reported) *Healing at 8 weeks* esomeprazole 40 mg: 67.6% lansoprazole 30 mg: 66.3% (p-value not reported)	5/499 (1%) esomeprazole vs 9/502 (2%) lansoprazole. Most common adverse event leading to study withdrawal was abdominal pain (two in each group)	Good	AstraZeneca

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Population, Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks
Gillessen, 2004	227 patients at 27 centers in Germany. Mean age 53 (SD 15) in pantoprazole group, 54 (SD 14) in esomeprazole group. 57% of pantoprazole, 50% of esomeprazole group male. 97% of pantoprazole, 98% of esomeprazole group Caucasian (others Asian)	Grade B: 84% pantoprazole, 83% esomeprazole Grade C: 16% pantoprazole, 17% esomeprazole (Los Angeles classification)	Screened NR/eligible NR/227 enrolled/227 analyzed ITT/197 analyzed per protocol	"Early time points" (4 and 6 weeks) Intention-to-treat (N=227): pantoprazole 40 mg: 74% esomeprazole 40 mg: 72% (NS) Per-protocol (N=197): pantoprazole 40 mg: 78% esomeprazole 40 mg: 74% (NS)

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Healing Rate at 8 Weeks	Symptoms at 4 Weeks	Symptoms at 8 Weeks
Gillessen, 2004	"Late time points" (8 and 10 weeks) Intention-to-treat (N=227): pantoprazole 40 mg: 90% esomeprazole 40 mg: 92% (NS) Per-protocol (N=197): pantoprazole 40 mg: 96% esomeprazole 40 mg: 93% (NS)	Overall relief of symptoms Per-protocol (N=197): pantoprazole 40 mg: 37% esomeprazole 40 mg: 35% (NS for PP or ITT)	Overall relief of symptoms Per-protocol (N=197): pantoprazole 40 mg: 47% esomeprazole 40 mg: 32% (NS for PP or ITT) After 10 weeks: pantoprazole 40 mg: 65% esomeprazole 40 mg: 63% (NS for PP or ITT)

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Results by Baseline Severity	Withdrawals Due to Adverse Events	Quality rating	Funding source
Gillessen, 2004	Per-protocol, overall healing by baseline grade Grade B: pantoprazole 40 mg: 92% esomeprazole 40 mg: 95% Grade C: pantoprazole 40 mg: 67% esomeprazole 40 mg: 45% Among patients diagnosed with grade C at baseline, 100% of pantoprazole and 91% of esomeprazole improved to Grade A or B at final visit.	6 patients overall, not reported by group.	Fair: Randomization, allocation concealment method not reported.	Altana Pharma, Germany

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Population, Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks
Kao et al, 2003	100 patients at one center in Taiwan mean age 49 69% male 100% Asian	Grade A: 51% Grade B: 49% (Los Angeles Classification)	Screened NR/eligible NR/100 enrolled	Not reported

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Healing Rate at 8 Weeks	Symptoms at 4 Weeks	Symptoms at 8 Weeks
Kao et al, 2003	Not reported	Esomeprazole 40 mg vs omeprazole 20 mg Per-protocol (N=91) Symptom-free on day 1: 28.2% vs 26.2% (NS) Symptom-free before week 1: 56.4% vs 55.6% (NS) Median days to symptom resolution: 4 vs 4 (NS) Achievement of sustained symptom response Week 1: 15.2% vs 15.6% (NS) Week 2: 50% vs 20% (p<0.05) Week 3: 71.7% vs 40% (p<0.01) Week 4: 73.9% vs 51.1% (p<0.05) Week 4 (intention-to-treat): 68% vs 46% (p<0.05)	Efficacy of on-demand therapy (n=34 esomeprazole 40 mg, n=23 omeprazole 20 mg, initiated week 5)

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Results by Baseline Severity	Withdrawals Due to Adverse Events	Quality rating	Funding source
Kao et al, 2003	Not reported	Not reported	Fair: not clear if patients masked, randomization, allocation concealment methods not reported.	Supported by a grant from the National Cheng Kung University

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Population, Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks
Castell 1996	1070 US patients at multiple centers (number excludes placebo), mean age 47, (range 18-84); 60-68.4% male; 85% white, 9% black, 5% Hispanic.	Grade 2: 61%-71% Grade 3: 24%-30% Grade 4: 6%-9% (See Appendix F for scale) 6.5%-8.7% Barrett's esophagus	1284 enrolled, 1226 analyzed (total with placebo)	lansoprazole 15 mg: 72.0% lansoprazole 30 mg: 79.6% omeprazole 20 mg: 87.0% lansoprazole 30 mg vs lansoprazole 15 mg p<.05 omeprazole 20 mg vs lansoprazole 15 mg p<.05 Other comparisons NS

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Healing Rate at 8 Weeks	Symptoms at 4 Weeks	Symptoms at 8 Weeks
Castell 1996	lansoprazole 15 mg: 75.2% lansoprazole 30 mg: 87.1% omeprazole 20 mg: 87.0% lansoprazole 30 mg vs lansoprazole 15 mg p<.05 omeprazole 20 mg vs lansoprazole 15 mg p<.05 Other comparisons NS	Not given	Median percentage of days with heartburn: lansoprazole 15 mg: 12.3% lansoprazole 30 mg: 8.6% omeprazole 20 mg: 11.8% Median percentage with heartburn: lansoprazole 15 mg: 9.3 lansoprazole 30 mg: 6.5 (not ITT) lansoprazole15 mg vs omeprazole 20 mg p<0.05 nights lansoprazole15 mg vs lansoprazole 30 mg p< days and nights All other comparisons NS

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Results by Baseline Severity	Withdrawals Due to Adverse Events	Quality rating	Funding source
Castell 1996	When healing rates were adjusted for baseline esophagitis grade, treatment comparison results were similar to those of the overall analyses. Patients with less severe esophagitis (grade 2) at baseline had higher rates with all the active treatments than those with more severe disease (grades 3 and 4). Healing rate at 4 weeks, lansoprazole 15 mg vs lansoprazole 30 mg vs omeprazole 20 mg, by baseline esophagitis grade: grade 2: 83.2% vs 89.4% vs 88.2% grades 3 and 4: 59.5% vs 73.5% vs 69.8% at 8 weeks, lansoprazole 15 mg vs lansoprazole 30 mg vs omeprazole 20 mg, by baseline esophagitis grade:: grade 2: 87.8% vs 94.3% vs 91.6% grades 3 and 4: 62.5% vs 85.3% vs 88.7%	omeprazole 20 mg: 2% lansoprazole 30 mg: 1.7% lansoprazole 15 mg: 0.9%	Fair: randomization and allocation method not reported, attrition not reported	Supported by TAP Pharmaceuticals, Inc.

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Population, Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks
Castell et al, 2002	5241 patients, multiple centers, mean age 47 (range 18-75), 57% male, 91% white, 6% black, 3% other.	Grade A: 36% Grade B: 40% Grade C: 18% Grade D: 6% (LA Grade) Heartburn Severity None: 1% Mild: 10% Moderate: 47% Severe: 42%	5241 enrolled, ITT Number screened NR lansoprazole 30 mg (n=2617) esomeprazole 40 mg (n=2624)	esomeprazole 79.4% lansoprazole 75.1% (p<.001) (life-table analysis)

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Healing Rate at 8 Weeks	Symptoms at 4 Weeks	Symptoms at 8 Weeks
Castell et al, 2002	EE esomeprazole 92.6% lansoprazole 88.8% (p=.0001) (life-table analysis)	Complete resolution of heartburn: lansoprazole 60.2% esomeprazole 62.9% (p<.05) Heartburn-free nights: lansoprazole 85.8% esomeprazole 87.1% (p<.05) Heartburn-free days: NS	Not reported

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Results by Baseline Severity	Withdrawals Due to Adverse Events	Quality rating	Funding source
Castell et al, 2002	esomeprazole 75.7% lansoprazole 71.7% (p<0.01, stratified by baseline severity) esomeprazole 87.6% lansoprazole 84.2% (p<0.01, stratified by baseline severity)	No difference in treatment-related adverse effects. Withdrawal due to adverse event 1.8% vs. 1.9%.	Good	Supported by AstraZeneca, also listed in author credits

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Population, Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks
Corinaldesi 1995	241 patients at 30 centers, Belgium, France, Italy, the Netherlands, median age 50-52, (range 18-88); 63% male; ethnicity not given.	Grade 2: 82% Grade 3: 18% (Savary-Miller)	Number screened not given, 241 randomized, 208 evaluable; 3 withdrew, 23 did not attend f/u.	pantoprazole 40 mg: 67.5% omeprazole 20 mg: 68.6% p=NS

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Healing Rate at 8 Weeks	Symptoms at 4 Weeks	Symptoms at 8 Weeks
Corinaldesi 1995	pantoprazole 40 mg: 80.8% omeprazole 20 mg: 79.3% p=NS	Heartburn free: omeprazole 20 mg: 82.2% pantoprazole 40 mg: 87.9% p=NS	Not reported

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Results by Baseline Severity	Withdrawals Due to Adverse Events	Quality rating	Funding source
Corinaldesi 1995	Not reported	pantoprazole 40 mg: 0.8% omeprazole 20 mg: 1.7%	Poor: randomization and allocation method not reported, no intention-to-treat analysis, baseline characteristics not analyzed.	Last author from Byk Gulden Pharma-ceuticals, study supported by same.

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Population, Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks
Dekkers 1999	202 patients of 27 investigators in 10 European countries, mean age 53 + 15.63, (range 20-86); 62% male; ethnicity not given.	Grade 2: 43% Grade 3: 52% Grade 4: 4% (modified Hetzel-Dent)	Number screened not given, 202 enrolled, 192 completed.	rabeprazole 20 mg: 81% omeprazole 20 mg: 81% (Not ITT) p=NS
Delchier 2000	300 patients of 61 investigators at 50 European centers, mean age 53 (+15), (range 18-80); 62% male; ethnicity not given.	Mean grade 2.6-2.7, median 3.9, (modified Hetzel-Dent) 7% had Barrett's esophagus, 41% positive for H. pylori	358 screened, 310 randomized, 298 completed.	rabeprazole 20 mg: 88.5% rabeprazole 10 mg: 85.4% omeprazole 20 mg: 91.2% p=NS

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Healing Rate at 8 Weeks	Symptoms at 4 Weeks	Symptoms at 8 Weeks
Dekkers 1999	rabeprazole 20 mg: 92% omeprazole 20 mg: 94% (Not ITT) p=NS	Heartburn frequency (resolution): rabeprazole 20 mg: 29.6% omeprazole 20 mg: 26.5% Daytime severity (resolution): rabeprazole 20 mg: 61.9% omeprazole 20 mg: 60.8% Nighttime severity resolution: rabeprazole 20 mg: 61.6% omeprazole 20 mg: 57.3% p=NS for all	Heartburn frequency resolution: rabeprazole 20 mg: 37.8% omeprazole 20 mg: 31.4% Daytime severity resolution: rabeprazole 20 mg:68.0% omeprazole 20 mg: 66.0% Nighttime severity resolution: rabeprazole 20 mg: 64.4% omeprazole 20 mg: 66.7% p= NS for all
Delchier 2000	rabeprazole 20 mg: 91.3% rabeprazole 10 mg: 91.3% omeprazole 20 mg: 94.2% p=NS	Severity of daytime and nighttime heartburn: p=NS (numbers not given)	Severity of daytime and nighttime heartburn: p=NS (numbers not given)

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Results by Baseline Severity	Withdrawals Due to Adverse Events	Quality rating	Funding source
Dekkers 1999	Not reported	rabeprazole 20 mg: 1% omeprazole 20 mg: 0	Fair: randomization and allocation method not reported intention-to-treat for symptoms only, not for healing.	Last author (corresponding author) and 5th authors with Eisai Ltd, funding info not given.
Delchier 2000	No statistically significant differences between treatment groups after controlling for baseline factors including Hetzel-Dent grade (other factors sex, age, smoking and H. pylori status); data not reported.	rabeprazole 10 mg: 5% rabeprazole 20 mg: 5% omeprazole 20 mg: 2%	Fair: randomization and allocation method not reported, followup somewhat high (76%-83%).	Funded by Eisai Ltd, London, last author (corresponding author) from Eisai

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Population, Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks
Dupas 2001	461 patients at 29 hospital centers and 45 private practices in France; mean age 54 (+14.6); 74% male; ethnicity not given	83% Grade 2 17% Grade 3 (Savary-Miller)	Number screened not given; 461 randomized, 385 completed	pantoprazole 40 mg ITT: 80.90% lansoprazole 30 mg ITT: 80% p=NS

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Healing Rate at 8 Weeks	Symptoms at 4 Weeks	Symptoms at 8 Weeks
Dupas 2001	pantoprazole 40 mg ITT: 89.80% lansoprazole 30 mg ITT: 90% p=NS	Symptom free (all symptoms - heartburn, acid regurgitation, pain or swallowing): ITT: pantoprazole 40 mg: 83% lansoprazole 30 mg: 92% p=NS	Not reported

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Results by Baseline Severity	Withdrawals Due to Adverse Events	Quality rating	Funding source
Dupas 2001	For both treatments, healing rates after 4 weeks were lower in grade III than in grade II esophagitis (69% vs 89%, per-protocol analysis, p=0.0001), with no grade-dependent significant differences between groups.	pantoprazole 40 mg: 13% lansoprazole 30 mg: 2.5%	Fair: randomized method not clear, allocation method not reported	Funded by BYK France, last author from BYK

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Population, Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks
Hatlebakk 1993	229 patients at 9 hospitals in Norway and Sweden; mean age 55; 66% male; ethnicity not given	lansoprazole 30 mg group: Grade 0: 2.6% Grade 1: 34.5% Grade 2: 50.9% Grade 3: 12.1% omeprazole 20 mg group: Grade 0: 2.7% Grade 1: 38.9% Grade 2: 55.8% Grade 3: 2.7% (See Appendix E for scale)	Number screened not given, 229 enrolled.	lansoprazole 30 mg: 61.2% omeprazole 20 mg: 64.6% p=NS
Holtmann, 2002	251 patients at multiple centers in Germany, Denmark, and Switzerland; mean age 52; 66% male, 99% Caucasian.	rabeprazole: 78% grade II, 22% grade III; omeprazole: 84% grade II, 16% grade III	274 screened/254 eligible, 251 enrolled/13 withdrawn or no valid data/4 lost to followup/251 analyzed	No difference between groups (data not reported)

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Healing Rate at 8 Weeks	Symptoms at 4 Weeks	Symptoms at 8 Weeks
Hatlebakk 1993	lansoprazole 30 mg: 81.9% omeprazole 20 mg: 85.0% p=NS	Data not given: states lansoprazole 30 mg had greater improvement in heartburn (p=0.03)	Data not given, but states no significant differences in any symptoms.
Holtmann, 2002	per protocol (N=200) rabeprazole 20 mg: 92.7% omeprazole 40 mg: 89.2% (NS)	Not reported for this time point; difference in relief from heartburn on day 4 not significant between groups.	Not reported for this time point.

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Results by Baseline Severity	Withdrawals Due to Adverse Events	Quality rating	Funding source
Hatlebakk 1993	At both 4 and 8 weeks, and irrespective of treatment, healing rates were higher for patients with grade 1 esophagitis than grade 2 (p<0.01, two-stage logistic regression analysis). Results by treatment group not reported.	omeprazole 20 mg: 0.9% lansoprazole 30 mg: 0	Poor: randomization and allocation method not reported, no intention-to-treat analysis, eligibility criteria not specified, some differences at baseline.	Not reported
Holtmann, 2002	Healing rate in patients with GERD grade III (N=45) 4 weeks: 84% rabeprazole vs 72.2% omeprazole (NS) 8 weeks: 88% rabeprazole vs 77.8% omeprazole (NS)	4/125 (3%) rabeprazole vs 2/126 (2%) omeprazole	Fair: Not clear if randomization method adequate, allocation concealment method not reported, more rabeprazole patients grade III esophagitis at baseline (22% vs 16%).	Funded by Eisai and Janssen-Cilag

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Population, Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks
Howden et al, 2002	284 patients at multiple centers, mean age 46.5 (range 19-78), 56% male, 80% white, 5% black, 15% other.	Grade 2: 61% Grade 3:30% Grade 4: 8% (see Appendix F for scale)	284 enrolled; # screened, eligible not reported, 277 evaluated lansoprazole 30 mg (n=139) esomeprazole 40 mg (n=138)	lansoprazole 30 mg vs esomeprazole 40 mg 77.0% vs 78.3% (p=NS)

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Healing Rate at 8 Weeks	Symptoms at 4 Weeks	Symptoms at 8 Weeks
Howden et al, 2002	lansoprazole 30 mg vs esomeprazole 40 mg 91.4% vs 89.1% (95% CI of difference -4.7, 9.2)	Not reported	Not reported

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Results by Baseline Severity	Withdrawals Due to Adverse Events	Quality rating	Funding source
Howden et al, 2002	Healing rate or improvement of 2 grades at 8 weeks by baseline grade, lansoprazole 30 mg vs esomeprazole 40 mg: Grade 2: 94.3% (82/87) vs 95.1% (77/81) Grade 3: 92.7% (38/41) vs 81.8% (36/44) Grade 4: 90.9% (10/11) vs 84.6% (11/13) Week 4 healing: healing or improvement of 2 grades of erosive esophagitis from baseline were comparable between treatment groups, regardless of baseline grade of esophagitis (data not reported).	2/143 (1.4%) lansoprazole vs 5/141 (3.5%) esomeprazole	Fair: randomization and allocation concealment methods not reported.	Supported by TAP Pharmaceuticals.

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Population, Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks
Kahrilas 2000	1960 US patients at 140 centers; mean age 46; 60% male; ethnicity not given.	Grade A: 33% Grade B: 40% Grade C: 19% Grade D: 7% (Los Angeles classification) 9.6% H. pylori	3354 screened, 1960 randomized. 44 did not complete study due to an adverse event and 115 for other reasons including loss to f/u and withdrawal of consent.	esomeprazole 40 mg: 75.9% esomeprazole 20 mg: 70.5% omeprazole20: 64.7% (cumulative life table rate) esomeprazole 20 mg vs omeprazole 20 mg p=0.09 esomeprazole 40 mg vs omeprazole 20 mg (p <0.05)

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Healing Rate at 8 Weeks	Symptoms at 4 Weeks	Symptoms at 8 Weeks
Kahrilas 2000	esomeprazole 40 mg: 94.1% esomeprazole 20 mg: 89.9% omeprazole 20 mg: 86.9% (cumulative life table rate) esomeprazole 40 mg vs omeprazole 20 mg p<0.001 esomeprazole 20 mg vs omeprazole 20 mg p<0.05	Resolution of heartburn esomeprazole 40 mg: 64.7% esomeprazole 20 mg: 61.0% omeprazole 20 mg: 57.2% esomeprazole 40 mg vs omeprazole 20 mg p=0.005 other comparisons NS	"Cumulative analysis at week 8 not done because pts could complete the study at week 4 with healed reflux esophagitis, even if symptoms were present"

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Results by Baseline Severity	Withdrawals Due to Adverse Events	Quality rating	Funding source
Kahrilas 2000	Greater efficacy of esomeprazole 40 mg vs omeprazole 20 mg at 4 weeks was consistent when adjusting for baseline esophagitis grade (data not reported).	esomeprazole 40 mg: 2% esomeprazole 20 mg: 2.6% omeprazole 20 mg: 2%	Fair: Randomization methods not reported, baseline characteristics not analyzed, more grade A patients (mild) in esomeprazole 40 mg group than omeprazole 20 mg group at baseline (35.9% esomeprazole vs 31.2% omeprazole 20 mg; calculated p = 0.07).	4 of 9 authors from Astra Zeneca, study supported by grant from Astra Zeneca.

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Population, Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks
Korner et al, 2003	669 patients at multiple centers, mean age 53.8 (sd 14), 60% male, ethnicity not reported.	84% Grade II 16% Grade III (Savary-Miller)	669 included; number screened, eligible not reported. Pantoprazole 40 mg (n=337) omeprazole MUPS 40 mg (n=332)	ITT results reported as odds ratios only. PP results, pantoprazole 40 mg (n=282) vs omeprazole MUPS 40 mg (n=270) 70.9% vs 72.6%
Labenz et al, 2005	3151 patients, multinational, mean age 50.6 (sd 14), 63% male, 97% Caucasian.	Grade A: 32% Grade B: 44% Grade C: 19% Grade D: 5% (LA Classification)	3170 randomized, 3151 analyzed. 9 excluded from analysis because of intake of an unknown study drug, and 10 because of study protocol violations.	**esomeprazole 40 mg vs pantoprazole 40 mg** Observed (per protocol): 78.8% vs 72.8% risk difference 6% (95% CI 3%, 9%) Life table analysis, per protocol: 81.0% vs 74.5% (p<0.001)

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Healing Rate at 8 Weeks	Symptoms at 4 Weeks	Symptoms at 8 Weeks
Korner et al, 2003	ITT results reported as odds ratios only. "Healing rates after 8 weeks of treatment were also similar in both groups."	ITT results not reported PP, pantoprazole 40 mg vs omeprazole MUPS 40 mg: Heartburn relief: 83.7% vs 88.1% Relief of pain on swallowing: 83.1% vs 91.9% (p-values not reported)	ITT results not reported PP, pantoprazole 40 mg vs omeprazole MUPS 40 mg: Heartburn relief: 91.1% vs 92.6% Relief of pain on swallowing: 94.1% vs 96.3% (p-values not reported)
Labenz et al, 2005	**esomeprazole 40 mg vs pantoprazole 40 mg** Observed (per protocol): 91.6% vs 88.9% risk difference 3% (95% CI 1%, 5%) Life table analysis, per protocol: 95.5% vs 92.0% (p<0.001)	**esomeprazole 40 mg vs pantoprazole 40 mg** Time to achieve sustained heartburn resolution (defined as the first of 7 consecutive days with no heartburn): 6 days vs 8 days (p<0.001)	**esomeprazole 40 mg vs pantoprazole 40 mg** Proportion of heartburn-free days: 70.7% vs 67.3% (p<0.01)

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Results by Baseline Severity	Withdrawals Due to Adverse Events	Quality rating	Funding source
Korner et al, 2003	Not reported (all patients were Grade II or III)	4/337 (1%) pantoprazole, 7/332 (2%) omeprazole MUPS	Fair: ITT results not reported, randomization and allocation concealment methods not reported.	Supported by a grant from ALTANA Pharma AG, Germany.
Labenz et al, 2005	Healing of esophagitis by baseline grade, esomeprazole 40 mg vs pantoprazole 40 mg Week 4, (Observed, per protocol): Grade A: 83.9% vs 83.1% (NS) Grade B: 80.2% vs 75.4% (p<0.05) Grade C: 71.1% vs 60.1% (p<0.01) Grade D: 61.4% vs 40.2% (p<0.01) Week 8 (Life table analysis, per protocol): Grade A: 97.3% vs 97.1% (NS) Grade B: 96.9% vs 93.1% (p<0.05) Grade C: 91.3% vs 87.6% (p<0.01) Grade D: 88.1% vs 73.6% (p<0.05)	2.1% esomeprazole, 1.8% pantoprazole	Fair/Poor: Randomization and allocation concealment methods not reported. Post-randomization exclusions (19 patients) and no data on excluded patients. Baseline data excludes 19 patients randomized but excluded due to intake of an unknown study drug or protocol violations. No data on excluded patients. Some differences in baseline esophagitis grade at baseline (grade B: 42.6% esomeprazole vs 45.1% pantoprazole; grade D: 4.5% esomeprazole, 5.8% pantoprazole).	AstraZeneca

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Population, Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks
Lightdale, 2006	1176 patients, multicenter, 63.6% male, 91.8% Caucasian, mean age 45 yrs	Grade A: 37% Grade B: 36.4% Grade C: 19% Grade D: 7.5% (LA clasification)	1876/NR/1106/47/23	Life table analysis: esomeprazole 20 mg vs. pantoprazole 20 mg 68.7% vs 69.5%

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Healing Rate at 8 Weeks	Symptoms at 4 Weeks	Symptoms at 8 Weeks
Lightdale, 2006	Life table analysis 90.6% vs. 88.3%, p=0.621 (log rank test)	esomeprazole vs omeprazole resolution of heartburn: 60.6 vs 60.5% ; p=0.995 Proprotion of heart burn free days: 72.6% vs. 70.9%p=0.354 Proportion of hear burn free nights: 85.7% vs. 83.2%, p=0.354	**NR**

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Results by Baseline Severity	Withdrawals Due to Adverse Events	Quality rating	Funding source
Lightdale, 2006	healing rate acroos baseline grade at week 8 20 mg esomeprazole vs 20 mg omeprazole Grade A: 94.6% vs. 87.7% Grade B: 85.0% vs 84.7% Grade C: 78.5% vs. 72.8% Grade D: 73.0% vs. 68.6% All: 86.5% vs 82.3% (p=0.052)	esomeprazole=1.5% omeprazole=1.7%	Good	AZ

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Population, Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks
Pace et al, 2005	549 patients, multi center Italy, mean age 47.4 (sd 14), male 68.1%	Grade 0: 1% Grade 1: 69% Grade 2: 24% Grade 3: 5.5% Grade 4: 0% (Savary-Miller)	Screened NR, Eligible NR, Enrolled 560, Withdrawn 47, lost to f/u 9	rabeprazole 20 mg: PP 91.0%, omeprazole 20 mg: PP 89.9%, equivalence bet. the two drugs is statistically significant (p<0.001)

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Healing Rate at 8 Weeks	Symptoms at 4 Weeks	Symptoms at 8 Weeks
Pace et al, 2005	rabeprazole 20 mg: PP 97.9%, omeprazole 20 mg: PP 97.5%, equivalence bet. the two drugs is statistically significant (p<0.0001)	ITT population, mean time to the first day w/ satisfactory heartburn relief, rabeprazole (n=271) 2.8+-0.2 days, omeprazole (n=271) 4.7+-0.5 days (p=0.0045), mean time to complete heartburn relief, rabeprazole 7.2 days, omeprazole 8.4 days (p=NS). Patients w/ complete heartburn relief (day and nighttime) in each day of first week of treatment (ITT patients) Rabeprazole n=245 32.2%, Omeprazole n=243 18.9%	NR

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Results by Baseline Severity	Withdrawals Due to Adverse Events	Quality rating	Funding source
Pace et al, 2005	Healing rates of oesophagitis grade at endpoint (4 or 8 weeks), rabeprazole vs omeprazole: grade I: 99.4 vs. 98.8%, grade II: 95.1 vs. 96.4%, grade III: 91.7 vs. 86.7% (PP patients)	No significant difference bet. Treatment groups in single adverse event occurring, with exception of headache (Omeprazole 4.8% and Rabeprazole 1.4%)	Fair. Lack of ITT analysis, exclusion of people (2%) at baseline.	Janssen-Cilag, Italy

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Population, Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks
Mee 1996	604 patients at multiple centers, UK and Ireland, mean age 53; 67% male; ethnicity not given.	Grade 1: 39% Grade 2: 44% Grade 3: 15% Grade 4: 2% (Savary-Miller)	604 enrolled, 565 eligible, 537 evaluable	lansoprazole 30 mg: 62% omeprazole 20 mg: 56.6% p=NS

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Healing Rate at 8 Weeks	Symptoms at 4 Weeks	Symptoms at 8 Weeks
Mee 1996	lansoprazole 30 mg: 75.3% omeprazole 20 mg: 71.1% p=NS	Not given	Improvement in daytime epigastric pain lansoprazole 30 mg: 85.9% omeprazole 20 mg: 72.5% Improvement in nighttime epigastric pain lansoprazole 30 mg: 85.9% omeprazole 20 mg: 67.3% p=NS (includes only pts who attended 8-week visit who reported baseline pain)

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Results by Baseline Severity	Withdrawals Due to Adverse Events	Quality rating	Funding source
Mee 1996	Healing of esophagitis by baseline grade, lansoprazole vs omeprazole: Week 4: Grade I: 79% vs 68% Grade II: 72% vs 62% Grade III: 45% vs 57% Grade IV: 43% vs 60% Week 8 (cumulative): Grade I: 92% vs 87% Grade II: 88% vs 81% Grade III: 73% vs 72% Grade IV: 50% vs 50% Esophagitis grade and treatment were included in a logistic regression model. Odds ratio of healing on lansoprazole compared with omeprazole was 1.46 (95% CI 0.87, 2.45)	Not reported	Good/Fair: Allocation concealment method not given.	1 of 2 authors from Lederle Laboratories, funding info not given.

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Population, Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks
Mulder 1996	211 patients at multiple centers in The Netherlands; mean age 55; 70% male; ethnicity not given.	Grade 1: 0.47% (1 patient) Grade 2: 68% Grade 3: 24% Grade 4A: 8% (Savary-Miller)	Number screened not given, 211 enrolled, 3 lost to followup, 3 withdrew for lack of efficacy, 1 withdrawn for receiving double dose.	lansoprazole 30 mg ITT 85.50% PP 86.20% omeprazole 40 mg ITT 79% PP 79.6% p=NS

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Healing Rate at 8 Weeks	Symptoms at 4 Weeks	Symptoms at 8 Weeks
Mulder 1996	lansoprazole 30 mg ITT: 93.40% PP 95.70% omeprazole 40 mg ITT: 90.50% PP 93.4% p=NS	lansoprazole 30 mg No symptoms: ITT: 73.60% omeprazole 40 mg No symptoms: ITT 71.40%	"Because of the low number of patients not healed at 4 weeks, analysis of symptoms was not performed at 8 weeks."

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Results by Baseline Severity	Withdrawals Due to Adverse Events	Quality rating	Funding source
Mulder 1996	Healing of esophagitis by baseline grade, lansoprazole vs omeprazole: Week 4: Grade II: 90.8% vs 88.1% Grade III/IV: 81.5% vs 70.6% overall: Grade II: 97.4% vs 98.5% Grade III/IV: 92.6% vs 85.3% (All NS)	None	Fair: randomization and allocation concealment not reported,	Supported by Hoechst Marion Roussel BV and Janssen-Cilag BV, Netherlands

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Population, Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks
Mulder et al. 2002	461 patients, multiple centers; mean age 51.2 (range 18-80);59% male; ethnicity NR	Savary-Miller class: I: 59% II: 29% III: 8% IVa: 4% Heartburn Severity None: 4% Mild: 22% Moderate: 45% Severe: 29%	461 enrolled Number screened NR omeprazole MUPS 20 mg (n=151) lansoprazole 30 mg (n=156) pantoprazole 40 mg (n=154)	NR

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Healing Rate at 8 Weeks	Symptoms at 4 Weeks	Symptoms at 8 Weeks
Mulder et al. 2002	NR	(omeprazole vs lansoprazole vs pantoprazole) Heartburn relief : 84% vs. 78% vs. 84% omeprazole vs lansoprazole 90% CI -1.44 to 13.24 pantoprazole vs lansoprazole 90% CI -1.07 to 13.49 Satisfied: 79% vs. 76% vs. 79%. omeprazole vs lansoprazole 90% CI -4.04 to 11.68 pantoprazole vs lansoprazole 90% CI -4.94 to 10.80 pantoprazole vs omeprazole 90% cI -4.12 to 7.13	(omeprazole vs lansoprazole vs pantoprazole) Heartburn relief : 87% vs. 81% vs. 89% pantoprazole vs omeprazole 90% CI -4.55 to 7.64 omeprazole vs lansoprazole 90% CI -0.79 to 12.81 pantoprazole vs lansoprazole 90% CI 0.94 to 14.17 Satisfied: 89% vs. 86% vs. 91% omeprazole vs lansoprazole 90% CI -2.68 to 9.69 pantoprazole vs lansoprazole 90% CI -0.97 to 10.99 pantoprazole vs omeprazole 90% CI -4.12 to 7.13

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Results by Baseline Severity	Withdrawals Due to Adverse Events	Quality rating	Funding source
Mulder et al. 2002	Symptom relief at 4 and 8 weeks was similar for each grade of esophagitis. Maintenance phase (with omeprazole 20 mg or 40 mg only, N=391): symptom relief with omeprazole 20 mg was independent of initial severity of esophagitis; the number of patients in the omeprazole 40 mg maintenance group (N=21) was too small to be divided by initial esophagitis grade.	No difference in AEs between groups. None considered treatment related. Total withdrawals due to AE: 6/461 (1.3%) Total AEs: 73/461 (15.8%)	Fair: randomization and allocation methods not reported. More withdrawals in L group.	Supported by AstraZeneca

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Population, Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks
Richter et al, 2001a	2425 patients at 163 US centers; mean age 47 (sd 12); 61% male; ethnicity 93.5% Caucasian.	Grade A: esomeprazole 40 mg 35%; omeprazole 20 mg 32% Grade B: esomeprazole 40 mg 39%; omeprazole 20 mg 42% Grade C: esomeprazole 40 mg 21%; omeprazole 20 mg 20% Grade D: esomeprazole 40 mg 5%; omeprazole 20 mg 7% (LA classification)	4798 screened, 2425 randomized; 109 did not complete: 24 for adverse events, 25 investigator-initiated decision, 25 lost to followup, 31 consent withdrawn, 4 lack of therapeutic response.	esomeprazole 40 mg vs omeprazole 20 mg cumulative life table rate: 81.7% vs 68.7% (p<0.001) Crude rates: 78.6% vs 66.6% (p = 0.001 for CMH test) risk difference 12% (95% CI 9%, 16%)

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Healing Rate at 8 Weeks	Symptoms at 4 Weeks	Symptoms at 8 Weeks
Richter et al, 2001a	esomeprazole 40 mg vs omeprazole 20 mg cumulative life table rate: 93.7% vs 84.2% (p<0.001) Crude rates: 89.9% vs 81.0% (p = 0.001 for CMH test) risk difference 9% (95% CI 6%, 12%)	esomeprazole 40 mg resolution of heartburn: 68.30% omeprazole 20 mg resolution of heartburn: 58.10%	"Cumulative analysis at week 8 not done because pts could complete the study at week 4 with healed reflux esophagitis, even if symptoms were present"

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Results by Baseline Severity	Withdrawals Due to Adverse Events	Quality rating	Funding source
Richter et al, 2001a	Greater efficacy of esomeprazole 40 mg vs omeprazole 20 mg at 4 weeks was consistent when adjusting for baseline esophagitis grade. Week 4 healing rates by baseline esophagitis grade (approximate, estimated from figure): esomeprazole 40 mg vs omeprazole 20 mg: Grade A: 88% vs 82% Grade B: 79% vs 66% Grade C: 71% vs 53% Grade D: 55% vs 35% Week 8 healing rates by baseline esophagitis grade (approximate, estimated from figure): esomeprazole 40 mg vs omeprazole 20 mg: Grade A: 93% vs 91% Grade B: 90% vs 82% Grade C: 88% vs 70% Grade D: 80% vs 62% (p=0.001 for CMH test, esomeprazole vs omeprazole)	1% in each group	Good	Supported by Astra Zeneca, one or more authors from Astra Zeneca.

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Population, Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks
Richter et al., 2001b	3510 patients, multiple centers, mean age 47 (range 18-89); 57% male, 88% white, 5% black, 7% other.	Grade 0: <1% Grade 1: 0% Grade 2: 68% Grade 3: 25% Grade 4: 7% (See Appendix F for scale)	3410 enrolled; number screened, eligible not reported.	Not evaluated

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Healing Rate at 8 Weeks	Symptoms at 4 Weeks	Symptoms at 8 Weeks
Richter et al., 2001b	Not evaluated	lansoprazole 30 mg vs omeprazole 20 mg Sustained resolution of heartburn: 77.2% vs 76.2% (p=NS)	lansoprazole 30 mg vs omeprazole 20 mg Sustained resolution of heartburn: 84.3% vs 83.0% (p=NS) More patients talking lansoprazole did not have a single episode of day or night heartburn (between 10% and 15%, p<0.05, data are presented graphically only)

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Results by Baseline Severity	Withdrawals Due to Adverse Events	Quality rating	Funding source
Richter et al., 2001b	Not reported	40/1754 (2%) lansoprazole 33/1756 (2%) omeprazole.	Fair: ITT results not reported, randomization and allocation concealment methods not reported.	Supported by a grant from TAP Pharmaceuticals

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Population, Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks
Scholten et al., 2003	217 patients at multiple centers, mean age 53 (sd ~14); 99% white	Grade B: 73% Grade C: 27% (LA Classification)	217 enrolled; number screened, eligible not reported.	Not evaluated

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Healing Rate at 8 Weeks	Symptoms at 4 Weeks	Symptoms at 8 Weeks
Scholten et al., 2003	Not evaluated	pantoprazole 40 mg vs esomeprazole 40 mg No or only mild heartburn: 99% vs 98%	Not evaluated

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Results by Baseline Severity	Withdrawals Due to Adverse Events	Quality rating	Funding source
Scholten et al., 2003	Not reported (all patients were Grade B or C)	3 patients discontinued due to adverse events not related to study drug (myocardial infarction, headache, allergic reaction). Groups not reported.	Fair: ITT results not reported, randomization and allocation concealment methods not reported.	Supported by a grant from ALTANA Pharma AG, Germany.

Evidence Table 2. Quality assessment of included trials

	Internal Validity					
Author, Year Country	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**
Adachi 2003	Method not reported	Yes	Yes	Yes	No- open	No
Ando 2005	Method not reported	Not reported	Some	Yes	Yes	Yes
Armstrong et al 2004	Method not reported	Not reported	Yes	Yes	Described as double-blind, not specified	Described as double-blind, not specified
Bardhan 2001	Method not reported	Not reported	More smokers in pantoprazole group (31% vs 22%), more males in omeprazole group (64% vs 52%)	Yes	No- open	No
Bardhan 2007	Yes	Yes	Yes	Yes	NR	Unclear, used identical appearance in shape and color medications

Evidence Table 2. Quality assessment of included trials

Author, Year Country	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions
Adachi 2003	No	Attrition and adherence yes	Yes- 20% of lansoprazole group lost to f/u for endoscopy 7% in other groups; but no loss to f/u for reporting of symptoms.	Yes for symptoms	No
Ando 2005	Yes	attrition yes, adherence no, crossovers no, contamination no	No	No	Yes
Armstrong et al 2004	Described as double-blind, not specified	No	Not reported	Unable to determine (defined as all randomized patients who took at least one dose of study medication and had post-randomization data, but number withdrawn not reported)	Unable to determine
Bardhan 2001	No	Attrition and adherence yes	No	Yes	No
Bardhan 2007	Yes	Attrition yes, others no	Somewhat, 29% pantoprazole and 27% esomeprazole withdrew	Yes	Yes, post randomization exclusions for protocol violation, but these people were included in ITT analysis

Evidence Table 2. Quality assessment of included trials

Author, Year Country	Quality Rating
Adachi 2003	Fair-poor
Ando 2005	Fair
Armstrong et al 2004	Fair
Bardhan 2001	Fair
Bardhan 2007	Fair

Evidence Table 2. Quality assessment of included trials

	Internal Validity					
Author, Year Country	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**
Bate 1995	Method not reported	Method not reported	Yes	Yes	Not reported	Not reported
Boccia 2007	Yes	Yes	Yes	Yes	Yes	Yes
Bour 2005	Randomization, method not described	No - open label	Mostly, except for on-demand group had fewer years with reflux	Yes	No - open label	No - open label
Bytzer 2004	Yes	Yes	Yes		Not reported	Yes
Bytzer 2006	Yes	Yes	Yes	Yes	NR	NR
Bytzer et al. 2004	Method not reported	Not reported	Yes	Yes	Yes	Yes

Evidence Table 2. Quality assessment of included trials

Author, Year Country	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions
Bate 1995	Yes	Attrition yes, others no	No	Yes	No
Boccia 2007	Yes	Attrition yes, others no	No - 1 patient withdrew	NR	NR
Bour 2005	No - open label	Attrition yes, others no	No; 13.2% total withdrew	Unclear, they state the conduct an ITT analysis, but in the results it is hard to see if they included the whole population in their analysis or not	No
Bytzer 2004	yes	Attrition yes, others no	No - placebo 24% and rabeprazole 13% withdrew but not LTF	Yes	No
Bytzer 2006	Yes	They mention how many people are in the PP vs the ITT analysis, but they do not account for the withdrawals in any way	Hard to tell, it appears as though 47% of rabeprazole and 50% of omeprazole groups withdrew, but hard to tell	Yes	Hard to tell, not sure why people are not in the PP analysis
Bytzer et al. 2004	Yes	Attrition yes, others no	No	No (analyzed patients who had data on at least 1 postrandomization visit; number not specified)	No

Evidence Table 2. Quality assessment of included trials

Author, Year Country	Quality Rating
Bate 1995	Fair
Boccia 2007	Fair-good
Bour 2005	Fair-poor
Bytzer 2004	Fair
Bytzer 2006	Fair (except it's hard to tell how people withdrew or who is in the PP analysis, so if that is a bigger deal for DERP I would rate this poor for that)
Bytzer et al. 2004	Fair

Evidence Table 2. Quality assessment of included trials

	Internal Validity					
Author, Year Country	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**
Caos 2000	Method not reported	Method not reported	No - placebo had higher baseline GERDheartburn frequency.	Yes	Not reported	Not reported
Caos 2005	Yes	Method not reported	Yes	Yes	Not reported	Not reported
Caos et al., 2005	Yes	Not reported	Yes	Yes	Yes	Yes
Chen, 2005	Yes	Not reported	omeprazole group older (59.0 vs 49.2, p=0.0596), more belching in esomeprazole group (47% vs 25.2%, p=0.0121)	Yes	Yes	Described as double-blind, not specified
Cibor 2006	Yes	NR	Yes	Yes	NR	NR
Cucchiara 1993	Method not reported	Not reported	Few given, some differences - clinical significance unclear	Yes	Some	No
Dent 1994	Yes, "computer generated randomization"	NR	Yes	Yes	NR	Implied - "double-blind"
Devault 2006	Yes	Yes	Yes	Yes	Unclear	Yes
Escourrou 1999	Yes	Method not reported	Yes	Yes	Not reported	Not reported

Evidence Table 2. Quality assessment of included trials

Author, Year Country	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions
Caos 2000	Described as double-blind, not specified	Attrition yes, others no	Yes - 43% rabeprazole 10 , 23% rabeprazole 20 and 79% placebo withdrew but not LTF	Yes	No
Caos 2005	Yes	Attrition and adherence yes	Yes - at 5 years R10 62%, R20 57% placebo 88% withdrew but not LTF	Yes	No
Caos et al., 2005	Yes	Attrition yes, others no	Not reported	Yes (LOCF)	No
Chen, 2005	Yes (placebo)	Attrition yes, others no	Not high (2), but not reported by group	No	No
Cibor 2006	NR	No	NR	NR	NR
Cucchiara 1993	No	Attrition yes, adherence no crossovers no, contamination no	19% drop-out, not differential but high	No	Yes
Dent 1994	Implied - "doubel-blind"	Attrition for open period yes, maintenance period hard to parse out, others no	Hard to parse out who withdrew. They only discuss who withdrew because of AEs.	They state they did an ITT analysis, but unable to parse out	NR
Devault 2006	Yes	Attrition yes, others no	No, 2% from esomeprazole and 3% from lansoprazole withdrew	Stated, but when you look at the number of peoeple on the table is the PP not the ITT population	Yes, they excluded 3% from esomeprazole and 3.5% from lansoprazole
Escourrou 1999	Yes	Attrition yes, others no	No	Yes	No

Evidence Table 2. Quality assessment of included trials

Author, Year Country	Quality Rating
Caos 2000	Fair
Caos 2005	Fair
Caos et al., 2005	Fair
Chen, 2005	Fair
Cibor 2006	Poor
Cucchiara 1993	Poor
Dent 1994	Poor
Devault 2006	Fair
Escourrou 1999	Fair

Evidence Table 2. Quality assessment of included trials

	Internal Validity					
Author, Year Country	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**
Fennerty 2005	Yes	Yes	Yes	Yes	Yes	Yes
Festen 1999	Yes	Method not reported	Yes	Yes	Not reported	Not reported
Florent 1994	Method not reported	Not reported	More patients with previous hemorrhage in O group	Yes	Unclear	Unclear
Fock et al., 2005	Yes	Method not reported	More women in esomeprazole group (57.8% vs 39.7%, p=0.051); otherwise similar	Yes	Described as double-blind, tablets inserted in identical capsules	Described as double-blind, tablets inserted in identical capsules
Gillessen 2004	Method not reported	Not reported	Yes	Yes	Yes	Yes
Glatzel 2006	Yes	Yes	Yes	Yes	Unclear	Unclear, used identical bottles, but not explicitaly stated
Goh 2007	Ransomization method not reported	NR	Yes	Yes	Unclear	"Double-blind" stated, but method not described

Evidence Table 2. Quality assessment of included trials

Author, Year Country	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions
Fennerty 2005	Yes	Attrition and adherence yes	No	Yes	1 in each group (did not take study medication)
Festen 1999	Yes	Attrition yes, adherence yes, crossovers no, contamination no	No	Yes	No
Florent 1994	Unclear	Attrition yes, adherence no, crossovers no, contamination no	14 (19%) excluded from analysis; 7% of L group and 15% of O group	No	Yes
Fock et al., 2005	Described as double-blind, tablets inserted in identical capsules	Attrition yes, others no	No	No (7 of 134 not analyzed)	Yes
Gillessen 2004	Yes	No	No	Yes	No
Glatzel 2006	Yes	Attrition yes, others no	No, 15% total, 14% pantoprazole and 16% esomeprazole withdrew	Yes	Yes, post randomization exclusions for protocol violation, but these people were included in ITT analysis
Goh 2007	"Double-blind" stated, but method not described	Attrition yes, others no	No, 13% total withdrew	Yes	No

Evidence Table 2. Quality assessment of included trials

Author, Year Country	Quality Rating
Fennerty 2005	Good
Festen 1999	Fair
Florent 1994	Poor
Fock et al., 2005	Fair
Gillessen 2004	Fair
Glatzel 2006	Fair
Goh 2007	Poor (randomization & allocation methods not described)

Evidence Table 2. Quality assessment of included trials

	Internal Validity					
Author, Year Country	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**
Hansen 2006	Method not reported	Method not reported	Yes	Yes	No - open study	No - open study
Hatlebakk 1993	Radomization, method not described	Yes, identical capsules	Mostly, except for more smokers received omeprazole and those who received lansoprazole had more severe heartburn	Yes	NR	Implied - "double-blind"
Hatlebakk 1997	Method not reported	Method not reported	Yes	Yes	Not reported	Not reported
Holtmann 2001	Not clear if adequate method	Not reported	22% of rabeprazole group Grade III vs 16.4% omeprazole	Yes	Yes	Yes
Houcke 2000	Randomization, method not described	Yes	Yes	Yes	NR	Implied - "double-blind"
Howden 2001	Yes	Yes	Yes	Yes	Not reported	Not reported
Inadomi 2003 - this study had only one arm so most questions are not applicable	Not applicable	Not applicable	Not applicable	Yes	Not applicable	Not applicable
Janssen, 2001	Yes	Yes.	Yes	Yes	No. Open label study	No. Open label study
Johnson 2001	Yes	Yes	Yes	Yes	Not reported	Not reported

Evidence Table 2. Quality assessment of included trials

Author, Year Country	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions
Hansen 2006	No - open study	None reported	Attrition or follow-up not reported	Yes	No
Hatlebakk 1993	Yes	Attrition yes, others no	No - 2% (6 patients)	NR	NR
Hatlebakk 1997	Yes	Attrition yes, others no	No	Yes	No
Holtmann 2001	Yes	Attrition yes	No	Yes	No
Houcke 2000	Yes	Attrition yes, others no	No - 19% withdew	Yes	NR
Howden 2001	Yes	Attrition yes, adherence yes, crossovers no, contamination no	No	Yes	No
Inadomi 2003 - this study had only one arm so most questions are not applicable	No	None reported	Not applicable	Yes	No
Janssen, 2001	No. Open label study	Yes, Others-No	lost to F/u in the long term phase 6.7%, No.	Yes (except for MDSL, where data was unavilable for 3 patients	No
Johnson 2001	Yes	Attrition yes, others no	Yes - 83% placebo 44% esomeprazole 10, 16% esomeprazole 20 and 24% esomeprazole 40 withdrew but not LTF	Yes	No

Evidence Table 2. Quality assessment of included trials

Author, Year Country	Quality Rating
Hansen 2006	Fair
Hatlebakk 1993	Fair
Hatlebakk 1997	Fair
Holtmann 2001	Fair
Houcke 2000	Fair
Howden 2001	Fair
Inadomi 2003 - this study had only one arm so most questions are not applicable	Poor
Janssen, 2001	Fair
Johnson 2001	Fair

Evidence Table 2. Quality assessment of included trials

	Internal Validity					
Author, Year Country	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**
Kao 2003	Method not reported	Not reported	Yes	Yes	Yes	Not reported
Kovacs 1999	Method not reported	Method not reported	No - Lansoprazole 30 weighed less (mean) and placebo arm had more day and night-time pain	Yes	Not reported	Not reported
Labenz 2005a	Method not reported	Not reported	Baseline data excludes 19 patients randomized but excluded due to intake of an unknown study drug or protocol violations. No data on excluded patients. Some differences in baseline esophagitis grade at baseline (grade B: 42.6% esomeprazole vs 45.1% pantoprazole; grade D: 4.5% esomeprazole, 5.8% pantoprazole)	Yes	Yes	Not reported
Labenz 2005b (Maintenance Therapy)	NR	NR	Yes	Yes	NR	NR
Laursen 1995	Yes	Method not reported	Yes	Yes	Described as double-blind, not specified	Described as double-blind, not specified
Lightdale, 2006	yes	Method NR	Yes	Yes	Yes	Described as double blind

Evidence Table 2. Quality assessment of included trials

Author, Year Country	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions
Kao 2003	Not clear	Attrition yes	No	Yes	No
Kovacs 1999	Yes	None reported	Not reported	yes	Yes - 4 were excluded due to NSAID use
Labenz 2005a	Yes	Adherence yes, others no	Not reported	No	Yes
Labenz 2005b (Maintenance Therapy)	NR	Attrition yes, Others no	No	No	Yes
Laursen 1995	Yes	Attrition yes, others no	No	Yes	Yes one patient had cancer and was excluded
Lightdale, 2006	Described as double blind	Attrition: Yes, crossovers:No, Adherence: Yes, Contamination: No	2.2%, No	Yes (only 1 person excluded for lack of EGD records for efficacy assessment)	yes. (only 1 person excluded)

Evidence Table 2. Quality assessment of included trials

Author, Year Country	Quality Rating
Kao 2003	Fair
Kovacs 1999	Poor- too small, post randomization exclusions, poor reporting
Labenz 2005a	Fair
Labenz 2005b (Maintenance Therapy)	Fair
Laursen 1995	Fair
Lightdale, 2006	Good

Evidence Table 2. Quality assessment of included trials

	Internal Validity					
Author, Year Country	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**
Lind 1999	Method not reported	Method not reported	Yes	Yes	Not reported	Not reported
Miehlke 2003	Yes	Not reported	Yes	Yes	No	No
Monikes et al., 2005	Method not reported	Method not reported	Yes	Yes	Described as double-blind, not specified	Described as double-blind, not specified
Moore 2003	Method not reported	Not reported	No	yes	Yes	Yes
Morgan 2007	Yes	Unclear	Yes	Yes	Unclear	Unclear
Norman Hansen 2005	Yes	Not applicable - open study	Yes	Yes	No - open study	No - open study
Pace 2005	Yes	centrally, but not clear where	yes(11 patients were omitted from baseline characteristic study)	yes	yes	yes
Peura et al., 2004	Yes	Method not reported	Yes (missing data on 1 lansoprazole, 1 placebo patient; h. pylori data missing on 6 patients)	Yes	Yes (patient diaries)	Described as double-blind, not specified

Evidence Table 2. Quality assessment of included trials

Author, Year Country	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions
Lind 1999	Method not reported	Attrition yes, adherence yes, crossovers no, contamination no	No	Yes	No
Miehlke 2003	No	Attrition yes, adherence yes, crossovers no, contamination no	7% esomeprazole vs 13% omeprazole	Yes	No
Monikes et al., 2005	Described as double-blind, not specified	Attrition and adherence yes, others no.	No	No (defined as those who took at least one dose of study medication), excluded 10 who did not meet interim eligibility criteria.	Yes (N=10 not eligible)
Moore 2003	Yes	attrition yes, adherence no crossovers no, contamination no	No; unclear	No	Yes
Morgan 2007	Unclear	Attrition yes, others no	No, 13% total withdrew	Yes	NR
Norman Hansen 2005	No - open study	Attrition yes, others no	Yes - omeprazole groups 10-11% ltf and ranitidine 40% withdrew but not LTF	Yes	No
Pace 2005	yes	attrition yes, others no	No	No; data available to calculate real ITT	unclear
Peura et al., 2004	Yes	No	Not reported	No	Yes (excluded if heartburn was predominant symptom)

Evidence Table 2. Quality assessment of included trials

Author, Year Country	Quality Rating
Lind 1999	Fair
Miehlke 2003	Fair-poor
Monikes et al., 2005	Fair
Moore 2003	Fair
Morgan 2007	Fair
Norman Hansen 2005	Fair
Pace 2005	Fair
Peura et al., 2004	Fair to Poor

Evidence Table 2. Quality assessment of included trials

	Internal Validity					
Author, Year Country	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**
Pilotto 2003	Method not reported	Method not reported	Not reported	Yes	Not reported	Not reported
Regula, 2006	Yes	Method not reported	Yes	Yes	decribed as double blind assured by identical appearance of capsules	decribed as double blind assured by identical appearance of capsules
Richter et al., 2004	Yes	Method not reported	Differences in race, otherwise similar	Yes	Not reported	Not reported
Robinson 1996	Yes	Method not reported	Yes	Yes	Method not reported	Method not reported
Schmitt 2006	Yes	Yes	Yes	Yes	Unclear, though implied	Yes
Schneider 2004	Yes	Yes	Mostly, the oral medication group had more men in it	Yes	NR	NR
Scholten 2007	Yes	NR	Yes	Yes	NR	NR

Evidence Table 2. Quality assessment of included trials

Author, Year Country	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	
Pilotto 2003	Method not reported	Attrition yes, others no	No	Yes	No	
Regula, 2006	decribed as double blind assured by identical appearance of capsules	Yes, Others-No	17.9% for pantoprazole 20mg, 14.6% for pantoprazole 40mg, 21% for omeprazole 20mg	yes for lack of "therapeutic failure"	No	
Richter et al., 2004	Yes	Attrition and adherence yes, others no	No	Yes	No	
Robinson 1996	Method not reported	Attrition yes, others no	Yes - 37% placebo 18% lansoprazole 15 and 16% lansoprazole 30	Yes for number of recurrance, can't tell for other outcomes		3
Schmitt 2006	Yes	Attrition yes, others no	No, 6% total, not broken down by groups	Yes	No	
Schneider 2004	Yes	Attrition yes, others no	No - 9% withdrew	Yes	NR	
Scholten 2007	NR	Attrition yes, others no	Somewhat, 23% total, 23% pantoprazole and 24% esomeprazole withdrew	Yes	No	

Evidence Table 2. Quality assessment of included trials

Author, Year Country	Quality Rating
Pilotto 2003	Poor - primarily due to lack of reporting especially baseline data at start of randomized phase
Regula, 2006	Fair (18% of patients were lost to follow-up)
Richter et al., 2004	Fair
Robinson 1996	Fair
Schmitt 2006	Good
Schneider 2004	Good
Scholten 2007	Fair

Evidence Table 2. Quality assessment of included trials

	Internal Validity					
Author, Year Country	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**
Sjostedt 2005	Yes	NR	Yes	Yes	NR	NR
Sontag 1996	Method not reported	Method not reported	Data not reported			Not reported
Sontag 1997	Method not reported	Method not reported	Data not reported for randomized portion	Yes	Not reported	Not reported
Stupnicki, 2003	Yes	Not reported	not clear- baseline characteristics given only for intention-to-treat population	Yes	Yes	Not reported
Talley, et al., 2001	Method not reported	Not reported	Yes	Yes	Described as double-blind, but not specified	Described as double-blind, but not specified
Tsai et al., 2004	Method not reported	Yes (sealed envelopes)	Yes	Yes	Yes? States "single blind (investigator)"	No? States "single blind (investigator)"
Vakil 2001	Yes	Yes	Yes	Yes	Yes	Yes
Vakil, 2004a	Yes	Yes	Yes	Yes	Yes	Yes
van Zyl et al., 2004	Yes	Method not reported	Yes	Yes	Described as double-blind, not specified	Described as double-blind, not specified

Evidence Table 2. Quality assessment of included trials

Author, Year Country	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions
Sjostedt 2005	NR	Attrition yes, others no	Somewhat, 23% total, 16% once daily and 31% on-demand withdrew	Yes	No
Sontag 1996	Not reported	Attrition yes, others no	Yes 30% lansoprazole and 70% placebo withdrew	Yes	17
Sontag 1997	Method not reported	None reported	Not reported	Yes	No
Stupnicki, 2003	Yes	Attrition yes	High (18%-19%) but not differential	Yes	No
Talley, et al., 2001	Yes	Attrition yes, others no	No	1 patient missing data	No
Tsai et al., 2004	No	Attrition and adherence yes, others no	No	Yes	No
Vakil 2001	Yes	Attrition yes, others no	Yes - 49% withdrew, but they analyze differences between those who discontinued and those who continued	No	NR
Vakil, 2004a	Yes	Attrition yes, adherence yes, crossovers no, contamination no	No	Yes	Yes
van Zyl et al., 2004	Yes	Attrition yes, others no	No	Yes	No

Evidence Table 2. Quality assessment of included trials

Author, Year Country	Quality Rating
Sjostedt 2005	Poor
Sontag 1996	Poor
Sontag 1997	Poor
Stupnicki, 2003	Fair
Talley, et al., 2001	Fair
Tsai et al., 2004	Fair
Vakil 2001	Fair-good
Vakil, 2004a	Fair
van Zyl et al., 2004	Fair

Evidence Table 2. Quality assessment of included trials

	Internal Validity					
Author, Year Country	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**
Vcev 2006	Not described, just stated as randomized	NR	Yes	Yes	NR	NR
Yang, 2003	Method not reported	Not reported	Yes	Yes	No	No

Evidence Table 2. Quality assessment of included trials

Author, Year Country	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions
Vcev 2006	NR	NR	No, but hard to tell, they don't discuss dropouts, just who is not included in the ITT analysis	Stated, but they excluded 4 people from the analysis due to (2) taking the wrong study medication and (2) for protocol violations	Yes, see ITT column
Yang, 2003	No	Attrition yes, adherence yes, crossovers no, contamination no	No	Yes	No

Evidence Table 2. Quality assessment of included trials

Author, Year Country	Quality Rating
Vcev 2006	Poor
Yang, 2003	Fair

Evidence Table 3. Nonerosive gastroesophageal reflux disease short-term trials

Author Year (Quality rating)	Population Setting	Inclusion criteria	Exclusion criteria	Number screened/ eligible/ enrolled
	Head-to -head trials			
Armstrong et al., 2004 (FAIR)	Endoscopy-negative N=2645 (in 3 trials) multicenter, parallel group	All patients who had experienced heartburn (defined as a burning feeling, rising from the stomach or lower part of the chest up towards the neck) as their main symptom for 6 months or longer, and for 4 days or more during the last week before the start of each study, and who had a normal endoscopy.	Not reported	NR/NR/NR

Evidence Table 3. Nonerosive gastroesophageal reflux disease short-term trials

Author Year (Quality rating)	Number withdrawn/ lost to followup/ analyzed	Results	Results
Armstrong et al., 2004 (FAIR)	NR/NR/2645	Patients with complete resolution of heartburn at 2 weeks (95% CI): Study A esomeprazole 40 mg: 34.6% (30.1%-39.3%) esomeprazole 20 mg: 39.7% (35.0%-44.6%) omeprazole 20 mg: 37.6% (33.0%-42.3%) Study B esomeprazole 40 mg: 41.2% (36.0%-46.6%) omeprazole 20 mg: 42.5% (37.2%-47.9%) Study C esomeprazole 20 mg: 41.4% (36.1%-46.8%) omeprazole 20 mg: 44.3% (38.9%-49.8%)	Patients with complete resolution of heartburn at 4 weeks (95% CI): Study A esomeprazole 40 mg: 56.7% (51.8%-61.5%) esomeprazole 20 mg: 60.5% (51.8%-61.5%) omeprazole 20 mg: 58.1% (53.3%-62.8%) Study B esomeprazole 40 mg: 70.3% (65.2%-75.1%) omeprazole 20 mg: 67.9% (62.7%-72.8%) Study C esomeprazole 20 mg: 61.9% (56.5%-67.1%) omeprazole 20 mg: 59.6% (54.1%-64.9%)

Evidence Table 3. Nonerosive gastroesophageal reflux disease short-term trials

Author Year (Quality rating)	Withdrawals Due to Adverse Events
Armstrong et al., 2004 (FAIR)	Not reported

Evidence Table 3. Nonerosive gastroesophageal reflux disease short-term trials

Author Year (Quality rating)	Population Setting	Inclusion criteria	Exclusion criteria	Number screened/ eligible/ enrolled
Fock et al., 2005 (FAIR)	Endoscopy-negative N=134 single center, parallel group	Age 21 to 65 years, with GERD symptoms (heartburn or regurgitation or both) present for at least 3 months in the previous year, which need not be continuous. Subjects needed to have experienced at least one period of moderate to very severe heartburn or regurgitation in the past 7 days prior to treatment. At endoscopy, no esophageal mucosal break was observed (i.e., grade 0 according to LA Classification)	Known history of gastroduodenal ulcer; infectious or inflammatory conditions of the intestine (including inflammatory bowel disease); malabsorption syndromes; obstruction; gastrointestinal malignancy; gastric or intestinal surgery including vagotomy; Barrett's esophagus; esophageal structure or pyloric stenosis; scleroderma; erosive esophagitis; positive HIV status and pregnancy. Abnormal laboratory tests at the initial visit (including liver enzymes greater than twice the upper limit of normal); GERD treatment refractory to a 2-month course of H2-blocker or PPI therapy; taken a PPI within 14 days of screening or a H2 blocker or prokinetic agent within 7 days of screening; required daily use of NSAIDs, oral steroids, aspirin (>325 mg/d); or were unable to discontinue the use of anticholinergics, cholinergics, spasmolytics, opiates, or sucralfate.	NR/NR/134

Evidence Table 3. Nonerosive gastroesophageal reflux disease short-term trials

Author Year (Quality rating)	Number withdrawn/ lost to followup/ analyzed	Results	Results
Fock et al., 2005 (FAIR)	7/0/127	Median time to first 24-hour symptom-free interval (heartburn) rabeprazole 10 mg: 8.5 days esomeprazole 20 mg: 9.0 days (NS) Median time to first 24-hour symptom-free interval (regurgitation) rabeprazole 10 mg: 6.0 days esomeprazole 20 mg: 7.5 days (NS) Percentage of patients achieving a 24-hour symptom-free interval (heartburn) rabeprazole 10 mg: 84.4% esomeprazole 20 mg: 60.9% (NS) Percentage of patients achieving a 24-hour symptom-free interval (regurgitation) rabeprazole 10 mg: 90.0% esomeprazole 20 mg: 67.9% (NS)	Patients with complete resolution of daytime heartburn at 1 week: rabeprazole 10 mg: 26.9% esomeprazole 20 mg: 23.4% (NS) Patients with complete resolution of nighttime heartburn at 1 week: rabeprazole 10 mg: 28.8% esomeprazole 20 mg: 20.9% (NS) Patients with complete resolution of daytime heartburn at 4 weeks: rabeprazole 10 mg: 55.3% esomeprazole 20 mg: 41.1% (NS) Patients with complete resolution of nighttime heartburn at 4 weeks: rabeprazole 10 mg: 44.4% esomeprazole 20 mg: 41.0% (NS)

Evidence Table 3. Nonerosive gastroesophageal reflux disease short-term trials

Author Year (Quality rating)	Withdrawals Due to Adverse Events
Fock et al., 2005 (FAIR)	1 (headache, esomeprazole)

Evidence Table 3. Nonerosive gastroesophageal reflux disease short-term trials

Author Year (Quality rating)	Population Setting	Inclusion criteria	Exclusion criteria	Number screened/ eligible/ enrolled
Monikes et al., 2005 (FAIR)	Endoscopy-negative N=529 multicenter, parallel group	Male and female, age 18 or older; patients had to have a history of frequent episodes of GERD-related symptoms during the last 3 months, and acid complaints for at least 3 days during the last week prior to study start; at least 3 episodes of acid complaints within the pre-treatment phase.	Any other gastrointestinal disease, erosive GERD (LA Grade A-D), Barrett's esophagus, acute peptic ulcer and/or ulcer complicatons, Zollinger-Ellison syndrome, pyloric stenosis, esophageal or gastric surgery, indication for H. pylori eradication therapy, and severe diseases of other major body systems. Pregnant and nursing women, or women of child-bearing potential who were not using reliable medical contraception; patients who had taken PPIs during the 10 days prior to study start, prokinetics or H2RAs during the 5 days prior to study start, or other substances for the relief of acid complaints, or systemic glucocorticosteroids, antiinflammatory drugs on more than 3 consecutive days, or PPI-based triple therapy for eradication of H. pylori during the last 28 days; intake of sculralfate during the 3 days prior to study start and concomitant intake of ketoconazole or other medication with pH-dependent absorption; regular intake of acetylsalicylic acid at doses up to 150 mg/day was permitted; patients also excluded if they showed poor compliance with regard to completing ReQuest.	574/564/539

Evidence Table 3. Nonerosive gastroesophageal reflux disease short-term trials

Author Year (Quality rating)	Number withdrawn/ lost to followup/ analyzed	Results	Results
Monikes et al., 2005 (FAIR)	78/NR/529	Mean time to first symptom relief (days) pantoprazole 20 mg: 5.9±8.1 esomeprazole 20 mg: 6.4+9.0 Mean time to sustained symptom relief (days) pantoprazole 20 mg: 13.2+11.6 esomeprazole 20 mg: 13.5+11.6 Patients reaching first symptom relief within 2 weeks pantoprazole 20 mg: 86.3% esomeprazole 20 mg: 84.5% Patients reaching sustained symptom relief within 2 weeks pantoprazole 20 mg: 56.4% esomeprazole 20 mg: 54.4% Patients reaching first symptom relief within 4 weeks pantoprazole 20 mg: 92.8% esomeprazole 20 mg: 89.7% Patients reaching sustained symptom relief within 4 weeks pantoprazole 20 mg: 80.2% esomeprazole 20 mg: 79.4%	

Evidence Table 3. Nonerosive gastroesophageal reflux disease short-term trials

Author Year (Quality rating)	Withdrawals Due to Adverse Events
Monikes et al., 2005 (FAIR)	Not reported

Evidence Table 3. Nonerosive gastroesophageal reflux disease short-term trials

Author Year (Quality rating)	Population Setting	Inclusion criteria	Exclusion criteria	Number screened/ eligible/ enrolled
	Placebo-controlled trials			
Peura et al., 2004	Endoscopy-negative N=921 multicenter, parallel group	At least 18 years of age, no history of documented or suspected gastroduodenal ulcers within the previous 5 years, and had symptoms of upper abdominal discomfort during the 3 months before the study.	Irritable bowel syndrome, taking more than two doses per week of an NSAID; upper GI endoscopy performed during screening period to exclude patients with erosive or ulcerative esophagitis. Excluded those with an active gastric or duodenal ulcer, duodenal erosion, or more than five gastric erosions. History of gastric or duodenal ulcer within the past 5 years; any other GI disease (including bleeding; gastric, duodenal, or esophageal surgery; esophageal structure requiring dilation; Barrett's esophagus); evidence of any uncontrolled disease involving major organ systems; laboratory results outside of the normal range; evidence of alcohol or drug abuse in the prior 12 months; use of chronic anticoagulant, antineoplastic, antidepressant, or corticosteroid therapy; treatment with an investigational agent within the prior 12 weeks; and use of a PPI, a prokinetic agent, any ulcerogenic drug, or aspirin within the prior 4 weeks.	NR/NR/921

Evidence Table 3. Nonerosive gastroesophageal reflux disease short-term trials

Author Year (Quality rating)	Number withdrawn/ lost to followup/ analyzed	Results	Results
Peura et al., 2004	NR/NR/NR	Difference from placebo in median percentage of days with upper abdominal discomfort after 8 weeks (95% CI): lansoprazole 15 mg: –10% (–16% to –5%) lansoprazole 30 mg: –9% (–15% to –4%) (NS) Change from baseline to 8 weeks in percentage of days with upper abdominal discomfort (95% CI): lansoprazole 15 mg: –10% (–16% to –5%) lansoprazole 30 mg: –9% (–15% to –4%) placebo: –9% (–15% to –4%) (NS)	

Evidence Table 3. Nonerosive gastroesophageal reflux disease short-term trials

Author Year (Quality rating)	Withdrawals Due to Adverse Events
Peura et al., 2004	

Evidence Table 3. Nonerosive gastroesophageal reflux disease short-term trials

Author Year (Quality rating)	Population Setting	Inclusion criteria	Exclusion criteria	Number screened/ eligible/ enrolled
	Active-controlled trials			
van Zyl et al., 2004	Symptomatic GERD (Endoscopy not conducted) N=338 multicenter, parallel group	Males and females, ages 18 to 75 with symptoms of heartburn, acid eructation, or pain on swallowing/dysphagia for 2 days prior to presentation. Presenting GERD symptoms were at least 2 points higher on the Likert scale (I.e., rather severe) than any other GI symptom (i.e., epigastric pain, vomiting, nausea, flatulence, retching, and retrosternal feeling of tightness). History of key GERD symptoms (one episode/month for at least 3 months) prior to entry into the study.	History of GI disease (e.g., peptic ulcer or ulcer complications, Zollinger-Ellison syndrome, esophageal strictures, or irritable bowel disease), concomitant severe disease (e.g., cardiovascular, respiratory and renal disorders, CND disorders, or malignant disease), or if they had any significant laboratory abnormalities. Women of child-bearing potential not taking reliable contraceptive measures, patients who had recently taken part in another clinical study, and patients who had recently taken or were still receiving PPI therapy or agents likely to affect gastric acid secretion or gut motility.	NR/NR/338

Evidence Table 3. Nonerosive gastroesophageal reflux disease short-term trials

Author Year (Quality rating)	Number withdrawn/ lost to followup/ analyzed	Results	Results
van Zyl et al., 2004	132/NR/338	Patients with relief from key GERD symptoms (heartburn, acid eructation, and pain on swallowing) after 4 weeks: pantoprazole 20 mg: 68.3% ranitidine 300 mg: 43.3% (95% CI for odds ratio 1.84 to 4.51)	

Evidence Table 3. Nonerosive gastroesophageal reflux disease short-term trials

Author Year (Quality rating)	Withdrawals Due to Adverse Events
van Zyl et al., 2004	

Evidence Table 4. Head-to-head trials of proton pump inhibitors for prevention of esophagitis relapse

Author Year	Population, setting	Esophagitis Grade (grading criteria), other characteristics	Number screened, eligible, enrolled, withdrawn, lost to followup
Caos 2005	Of 497 enrolled patients, 261 patients completed (Phase 1) and 205 patients completed (Phase 2.) Eligible patients were those with endoscopically confirmed healed erosive or ulcerative GERD ≤90 days prior to study entry. Mean age: Rabeprazole 20mg, 54.83 yrs; Rabeprazole 10 mg, 54.32 yrs; placebo 52.70 yrs Gender: Rabeprazole 20mg, 65% male; Rabeprazole 10 mg, 66.1% male; placebo 62.1% male Race: Rabeprazole 20mg: 86.5% Caucasian, 10.4% African-American, 3.1% other; Rabeprazole 10mg: 90.9% Caucasian, 4.8% African-American, 1.2% Asian, 3.0% other; Placebo: 92.9% Caucasian, 3.6% African-American, 1.2% Asian, 2.4% other	NR	NR/NR/497/236(Phase 1)/NR
Carling 1998	248 patients at 23 centers in Denmark, Finland, and Sweden; mean age 56 (+/- 12); 62% male; ethnicity not given	Grade 2: 72% Grade 3: 22% Grade 4: 6% (Savary-Miller)	289 treated , 262 healed, 248 continued to maintenance phase, 226 included in per protocol analysis.

Evidence Table 4. Head-to-head trials of proton pump inhibitors for prevention of esophagitis relapse

Author Year	Population, setting	Esophagitis Grade (grading criteria), other characteristics	Number screened, eligible, enrolled, withdrawn, lost to followup
Devault 2007	In the US at 143 centers; two groups included - patients with healed EE from a trial of patients with LA grades C or D EE who were treated with esomeprazole 40 mg once daily or lansoprazole 30 mg once daily for up to 8 weeks. The second group of patients included those with LA grades A or B EE who did not qualify for inclusion in the above trial. They received open-label treatment with esomeprazole 40 mg once daily for up to 8 weeks. Those whose EE was considered healed on the basis of an esophagogastroduodenoscopy (EGD) at week 4 and who reported no heartburn or acid regurgitation symptoms during the previous 7 days were eligible for randomization into this maintenance trial. Mean age 48 years 41% female 78% white 6% black 16% other	LA classification, % Grade A 37% Grade B 38% Grade C 20% Grade D 4.5%	4015 screened, 1026 randomized to trmt, 1001 ITT
Jasperson 1998	30 patients in Germany whose esophagitis healed after 6-8 weeks of omeprazole; mean age 57; 60% male; ethnicity not given.	All Grade 4 (Savary-Miller)	36 treated, 6 did not heal, 30 included.

Evidence Table 4. Head-to-head trials of proton pump inhibitors for prevention of esophagitis relapse

Author Year	Population, setting	Esophagitis Grade (grading criteria), other characteristics	Number screened, eligible, enrolled, withdrawn, lost to followup
Labenz et al 2005	2766 patients (63% men; mean age 50 years) were required to have EE [photographically documented at baseline endoscopy; Los Angeles (LA) grades A–D] within the 7 days preceding study randomization, a history of GERD symptoms for at least 6 months immediately prior to randomization, and heartburn with an overall severity of moderate or severe on at least 4 days in the week preceding randomization. This multicentre study was conducted at 263 centres in 14 countries.	LA grade A: 32.5% B: 44.4% C: 18.6% D: 4.6% H. pylori positive: 27.2%	Discontinuations due to adverse events (DAE) were reported for 19 patients (1.4%) in the esomeprazole 20 mg group and 18 patients (1.3%) in the pantoprazole 20 mg group.

Evidence Table 4. Head-to-head trials of proton pump inhibitors for prevention of esophagitis relapse

Author Year	Population, setting	Esophagitis Grade (grading criteria), other characteristics	Number screened, eligible, enrolled, withdrawn, lost to followup
Lauritsen et al. 2003	1224 patients in Europe and South Africa with history of heartburn and endo-verified GERD. Mean age: 49 Male: 61% White: 98%	LA grade A: 38% B: 45% C: 14% D: 3% H. pylori positive: 31%	1391 enrolled in healing phase, 1236 (89%) randomized for maintenance treatment. ITT = 1224 (615 esomeprazole, 609 lansoprazole). Healing phase: 31/1391 (2.2%) withdrawn for AE; 63 (4.5%) lack of therapeutic response; 61 (4.4%) lost, excluded, other. Randomized pop. exclusion: 12/1236 (0.1%) excluded from ITT for noncompliance or persistent esophagitis at entry. Maintenance phase: 51/1236 (4.1%) withdrawn for AE; 124 (10.0%) lack of therapeutic response; 50 (4.0%) lost, other. Similar AE profiles between groups.

Evidence Table 4. Head-to-head trials of proton pump inhibitors for prevention of esophagitis relapse

Author Year	Population, setting	Esophagitis Grade (grading criteria), other characteristics	Number screened, eligible, enrolled, withdrawn, lost to followup
Richter et al., 2004	349 patients at 32 sites in the US with either endoscopically confirmed healing of erosive esophagitis in prior acute pantoprazole or other regimen studies (omeprazole, lansoprazole, nizatidine, ranitidine) with confirmed healing at least 1 mo prior to start of study, patients who previously participated in acute studies with no healing; patients with Grade 2 or greater EE who did not participate in acute studies. Patient characteristics: mean age 49.56 yrs; 72.8% male; 90.5% white, 4.3% black, 4.3% Hispanic, 0.3% Asian, 0.6% other	Hetzel-Dent Scale Baseline (n=328): Grade 0: 69.6% Grade 1: 30.4% Acute baseline (n=321): Grade 2: 67.7% Grade 3: 25.0% Grade 4: 7.3%	349 enrolled/178 discontinued by 1 yr including 110 due to lack of efficacy and 19 due to adverse events. Discontinuations due to lack of efficacy most common among pantoprazole 10 mg patients (n=36) and ranitidine 150 mg patients (n=46)
Scholten 2007	Seven German centers, 236 patients with mild GORD were treated for 4 weeks w/ pantaprazole for 28 days, those w/out heartburn for last 3 days were randomized for on-demand treatment -199 ITT (Pantaprazole 99 esomeprazole 100, 153 PP) 49% female, 99.5% caucasian, 16% Helicobacter pylori positive,	59% LA grade A. 34% LA grade B 7% enGORD,	262 screened, 236 in acute phase, Patients without heartburn during the final 3 days of the AP randomized, 200 in long term phase (ITT 199)

Evidence Table 4. Head-to-head trials of proton pump inhibitors for prevention of esophagitis relapse

Author Year	Population, setting	Esophagitis Grade (grading criteria), other characteristics	Number screened, eligible, enrolled, withdrawn, lost to followup
Thjodleifsson et al. 2000 Thjodleifsson et al. 2003	243 patients at 21 centers in Europe with a previous diagnosis of erosive GERD healed within 90 days of enrollment; mean age 52.7 (+/- 14.3); 67% male; ethnicity not given.	Grade 0: 77% Grade 1: 22% 1 missing (modified Hetzel-Dent)	210/243 completed one year; 13 withdrew due to adverse events. 123 completed 5 years; 26 withdrew due to adverse events. No differences between groups.

Evidence Table 4. Head-to-head trials of proton pump inhibitors for prevention of esophagitis relapse

Author Year	Results	Quality rating	Funding source and role of funder
Caos 2005	*Primary endpoint:* Relapse rates at 5 yrs were 11% for rabeprazole 20mg, 23% for rabeprazole 10mg and 63% for placebo (p<0.001) Kaplan-Meier probability of GERD erosions being healed at 5 yrs: 87% rabeprazole 20mg, 33% for 10mg, 20% for placebo. No SS difference in relapse based on age. *Secondary endpoints:* Daytime heartburn relapse lower with both doses of rabeprazole v placebo (p<0.001 for 20mg, p≤0.018 10 mg) Night-time relapse rates favored rabeprazole 20mg (p≤0.005)	Fair	Supported by Eisai Inc and Janssen Pharmaceuticals
Carling 1998	*Endoscopic relapse by 48 weeks:* lansoprazole 30 mg: 8.7% omeprazole 20 mg: 8.2% *Symptomatic relapse by 48 weeks:* lansoprazole 30 mg: 0.8% omeprazole 20 mg:1.6% p=NS	Fair: allocation concealment not reported, more excluded from lansoprazole group at entry, more Grade 2 in lansoprazole group at baseline.	Supported by Wyeth Ayerst and Wyeth Lederle

Evidence Table 4. Head-to-head trials of proton pump inhibitors for prevention of esophagitis relapse

Author Year	Results	Quality rating	Funding source and role of funder
Devault 2007	Estimated remission rates through 6 months, % (95% CI) esomeprazole vs lansaprazole Endoscopic/symptomatic remission rate 84.8 (81.5–88.1) vs. 75.9 (72.0–79.8) p = .0007 Endoscopic remission rate 86.9 (83.8–90.1) vs. 77.8 (74.0–81.6) p = 0.0003 Observed and cumulative endoscopic/symptomatic remission rates, n (%) Month 3 (observed) 465 (92.8) vs. 434 (86.8) p <.0.0001 Month 6 (cumulative) 432 (86.2) vs. 388 (77.6) p < 0.0001	Fair	Supported by AstraZeneca
Jasperson 1998	*Endoscopic remission at 4 weeks:* omeprazole 20 mg: 90% lansoprazole 30 mg: 20% pantoprazole 40 mg: 30% *Recurrence of reflux symptoms at 4 weeks:* omeprazole 20 mg: 10% lansoprazole 30 mg: 60% pantoprazole 40 mg: 60% omeprazole vs lansoprazole p<0.01 omeprazole vs pantoprazole p<0.01	Fair: allocation concealment not reported, blinding of patients not reported, very small sample size. There was selection bias.	Not reported.

Evidence Table 4. Head-to-head trials of proton pump inhibitors for prevention of esophagitis relapse

Author Year	Results	Quality rating	Funding source and role of funder
Labenz et al 2005	*Primary endpoint:* Endoscopic plus symptomatic remission for all patients at 6 mos was 74.9% for 20 mg pantoprazole and 87.0% for 20 mg esomeprazole. *Secondary endpoint:* Esomeprazole 20 mg was significantly more effective than pantoprazole 20 mg for maintaining pure endoscopic healing of EE (6-month life table estimates: 88.1%; 95% CI: 86.3–90.0 vs. 76.6%; 95% CI: 74.2–79.0, log-rank test P < 0.0001).		Supported by a grant from AstraZeneca R&D, Sweden.

Evidence Table 4. Head-to-head trials of proton pump inhibitors for prevention of esophagitis relapse

Author Year	Results	Quality rating	Funding source and role of funder
Lauritsen et al. 2003	*Endoscopic remission at 6 months.* esomeprazole 84% vs. lansoprazole 76% (p<.0002)	Fair: small differences at baseline (slightly > males on esomeprazole slightly more H. pylori positive on lansoprazole); not ITT: 12 randomized but not included in ITT analysis for not taking any study drug OR persistent esophagitis at baseline (combined); 4 in esomeprazole group, 8 in lansoprazole group.	Sponsored by AstraZeneca

Evidence Table 4. Head-to-head trials of proton pump inhibitors for prevention of esophagitis relapse

Author Year	Results	Quality rating	Funding source and role of funder
Richter et al., 2004	*Primary endpoint:* Maintained EE healing at 12 mos was 78% for 40 mg pantoprazole; 55% for 20 mg pantoprazole; 46% for 10 mg pantoprazole and 21% for ranitidine 150 mg. 76% of Grade 2 and 72% of Grade 3/4 patients remained healed with pantoprazole 40mg, while 78%, 59% and 21% of Grade 2 patients remained healed with pantoprazole 20mg, pantoprazole 10 mg and ranitidine 150 mg respectively. *Secondary endpoints:* No SS difference of healing maintenance based on h.pylori status; more symptom-free days with pantoprazole 40 mg (83%) than with pantoprazole 10 mg (65%) or ranitidine (58%); less rescue medication use during first 4 mos of study for all pantoprazole doses vs ranitidine (p<0.05)	Fair	Supported by Wyeth
Scholten 2007	Mean intensity of heartburn Pantoprazole 1.12 vs.. Esomeprazole 1.32 p = 0.012 Combined symptom score of heartburn, acid eructation and pain on swallowing Pantoprazole 1.72 vs.. Esomeprazole 1.99 p = NS Number relief tablets taken - daily average (total) pantaprazole 0.35 (58.1) vs. esomeprazole 0.35	Fair	Supported by ALTANA Pharma AG,

Evidence Table 4. Head-to-head trials of proton pump inhibitors for prevention of esophagitis relapse

Author Year	Results	Quality rating	Funding source and role of funder
Thjodleifsson et al. 2000 Thjodleifsson et al. 2003	*Endoscopic relapse at 13 weeks:* rabeprazole 10 mg: 1.2% rabeprazole 20 mg: 2.6% omeprazole 20 mg: 1.2% *Endoscopic relapse at 26 weeks:* rabeprazole 10 mg: 1.2% rabeprazole 20 mg: 3.8% omeprazole 20 mg: 1.2% *Endoscopic relapse at 52 weeks:* rabeprazole 10 mg: 4.9% rabeprazole 20 mg: 3.8% omeprazole 20 mg: 4.8% Endoscopic relapse at 5 years: rabeprazole 10 mg: 9.8% rabeprazole 20 mg: 11.5% omeprazole 20 mg: 13.3% p=NS for all comparisons	Fair: allocation concealment not reported, not clear if maintenance of comparable groups.	Funded by Eisai, Ltd, UK

Evidence Table 5. Non-erosive gastroesophageal reflux disease relapse prevention

Author Year	Population, setting	Heartburn severity, other characteristics	Number screened, eligible, enrolled, withdrawn, lost to followup
Bytzer et al., 2004	535 patients at centers in Greece, Italy, the Netherlands, Spain, France, Portugal, Sweden, Denmark, Ireland, Belgium, United Kingdom, Russia, Poland and Lithuania; mean age: 47; 60% female; ethnicity not given	Patient assessment of heartburn severity scored on 5-point Likert scale; Quality of life assessed with 22-item Psychological General Well-being Index (PGWBI); 100% patients previously achieved complete relief of symptoms during acute treatment phase	668 screened Acute phase: 535 enrolled, 117 withdrawn, 5 lost to followup On-demand phase: 418 enrolled, 71 withdrawn, 9 lost to followup
Talley, et al., 2001	342 patients in 65 centers in Denmark, Finland, Norway and Sweden; mean age: 49; 56% male; ethnicity not given	Heartburn frequency and severity, and severity of related gastrointestinal symptoms with assessed with standardized checklist; 100% patients previously achieved complete relief of symptoms during acute treatment phase	342 enrolled, 123 withdrawn, 2 lost to followup
Tsai et al., 2004	774 enrolled patients, of whom 152 withdrew prior to randomization in 92 general practices and 28 hospitals with at least a 6 mo history of heartburn, including 4 of 7 days preceding study entry and no esophageal mucosal breaks verified by endoscopy up to 14 days prior to enrollment. Patient characteristics: mean age 51.3 yrs; 56% female; ethnicity NR	Severity of heartburn at baseline: Mild: 26.6% (n=195) Moderate: 59% (n=452) Severe: 15.4% (n=118) (n=765 total)	774 enrolled, 152 discontinued prior to randomization into maintenance phase of study, including 18 withdrawals due to AEs, 124 who did not meet eligibility and 10 for other reasons not specified. 622 randomized into maintenance phase, 80 withdrawals during maintenance phase due to adverse event, heartburn or other unspecified reason.

Evidence Table 5. Non-erosive gastroesophageal reflux disease relapse prevention

Author Year	Results	Quality rating	Funding source and role of funder
Bytzer et al., 2004	*Complete relief of symptoms at acute phase by 4 weeks:* rabeprazole 10 mg: 83% *Discontinuation due to lack of heartburn control during on-demand phase by 6 months:* rabeprazole 10 mg: 6% placebo: 20% p < 0.00001	Fair	Supported by Janssen Pharmaceutica
Talley, et al., 2001	*Discontinuation due to lack of heartburn control during on-demand phase by 6 months:* esomeprazole 20 mg: 14% placebo: 51% *Mean number of days patients remained with on-demand therapy:* esomeprazole 20 mg: 165 placebo: 119	Fair	Supported by AstraZeneca
Tsai et al., 2004	More lansoprazole 15 mg continuous use vs esomeprazole 20 mg on-demand unwilling to continue use at 6 mos (13% v 6%; p=0.001; 95% CI 9.2-16.8 and 2.8-8.8 respectively.) More esomeprazole patients were satisfied (score of 1-4 on Treatment Satisfaction Questionnaire) at 1 mo compared to lansoprazole patients (93.2% v 87.8%, p=0.02 95% CI 0.88-10.1) The difference in patient satisfaction between the treatment groups lessened at 3 and 6 mos, but exact percentages are not provided in the study.	Fair	Supported by Astra-Zeneca UK

Evidence Table 6. Randomized controlled trials of esophagitis treatment in children

Author Year Setting	Age, Gender, Race, Other Population Characteristics	Interventions	Control	Number Screened/ Eligible/ Enrolled
Moore 2003 South Australia	Mean age 5.4 mo 76% male 100% with gastroesophageal reflux and/or esophagitis, history of frequent spilling, irritability/crying level concerning to parents, previous treatment with pharmacologic treatment for GER	Omeprazole 10mg daily for infants 5-10kg, 10mg twice daily for infants >10kg	Matching placebo	64 eligible 34 enrolled
Cucchiara 1993 Italy	Age range 6 mo-13.4 yrs 50% male 100% diagnosis of GOR oesophagitis, unresponsive to previous antireflux treatment	Omeprazole 40mg/daily or ranitidine 20mg/kg/daily	Ranitidine 20mg/kg/daily	32 enrolled

Evidence Table 6. Randomized controlled trials of esophagitis treatment in children

Author Year Setting	Outcomes reported (results)	Number of adverse effects	Quality rating
Moore 2003 South Australia	***Parent daily diary mean scores of cry/fuss time in min/24h:*** *Baseline:* O: 246 vs placebo: 287 *Period 1 (2 weeks):* O: 203 vs placebo: 204 *Period 2 (2 weeks):* O: 179 vs placebo: 198 ***Visual Analog Scale mean scores of infant irritability:*** *Baseline:* O: 7.1 vs placebo: 6.6 *Period 1 (2 weeks):* O: 5.9 vs placebo: 6.0 *Period 2 (2 weeks):* O: 4.0 vs placebo: 5.7	None reported	Fair
Cucchiara 1993 Italy	***Healing rates:*** 0: 9(32%) vs R: 8(36%) ***Median percentage of improvement of intraoesophageal and intragastric pH variables:*** *Time of oesophageal pH <4.0:* O: 61.9 vs R: 59.6 *Time of intragastric pH <4.0:* O: 29.0 vs R: 22.3 *Time of intragastric pH <2.0:* O: 61.5 vs R: 62.2 *Median intragastric pH:* O: 60.1 vs R: 37.4 *Intragastric hydrogen activities (mmol/l):* O: 97.9 vs R: 91.0	No serious events requiring discontinuation of treatment observed	Poor

Evidence Table 7. Randomized controlled trials of duodenal ulcer treatment: Proton pump inhibitor compared with proton pump inhibitor

Author Year Setting	Age, Gender, Race Other Population Characteristics	Intervention	Control	Number
Beker 1995 Multicenter	Median age 44 (range 20 - 86) 70% male 50% smokers 20% alcohol users 58% 2 or more previous ulcers	Pantoprazole 40 mg once daily x 2 to 4 weeks	Omeprazole 20 mg once daily x 2 to 4 weeks	270 enrolled (135 each group)
Capurso 1995 Italy Multicenter	Reported as 'balanced' for age, sex, weight, smokers, alcohol use, ulcer history, symptoms, ulcer size, and prior complications	Lansoprazole 30 mg a day (morning) x 2 to 6 weeks	Omeprazole 20 mg once daily x 2 to 6 weeks	107 enrolled, (52 lansoprazole, 55 omeprazole)
Chang 1995 Taiwan Single center	Mean age 57 and 61 89% male 47% smokers 93% H. pylori positive	Lansoprazole 30 mg once daily x 4 weeks	Omeprazole 20 mg once daily x 4 weeks	83 enrolled (42 lansoprazole, 41 omeprazole)

Evidence Table 7. Randomized controlled trials of duodenal ulcer treatment: Proton pump inhibitor compared with proton pump inhibitor

Author Year Setting	Outcomes Reported (Results)	Number of Adverse Effects	Quality Rating
Beker 1995 Multicenter	*Healing:* *(PP analysis)* *2 weeks:* 71% pantoprazole, 65% omeprazole (p=0.31) *4 weeks:* 95% pantoprazole, 89% omeprazole (p= 0.09) ITT analysis results reported as 'similar' *Symptoms:* *Pain free (of those with pain at baseline)* *2 weeks:* 81% pantoprazole, 82% omeprazole (p = 0.87) *Patient diary:* no significant differences in time course of becoming pain free.	21 patients reported adverse events (10 pantoprazole, 11 omeprazole), with a total of 23 events reported. Diarrhea was the most common adverse event reported. 5 were considered serious (1 pantoprazole, 4 omeprazole). 3 in the omeprazole group were considered possibly related to study treatment (1 angina pectoris, 1 hypertension, 1 vertigo) and patients were withdrawn from study. The other 2 were GI hemorrhage pantoprazole, and abdominal pain omeprazole and considered not related to study drugs. No clinically significant changes in lab values from baseline values. Serum gastrin levels rose in both groups at both 2 and 4 weeks, the change was statistically significant within but not between groups.	Fair
Capurso 1995 Italy Multicenter	*Healing rates:* *2 weeks:* 58% lansoprazole, 57% omeprazole *4 weeks:* 94% lansoprazole, 94% omeprazole *Nighttime pain free:* *2 weeks:* 94% l), 87% omeprazole (NS) *Daytime Pain free* *2 weeks:* 92% lansoprazole, 81% omeprazole (NS)	8 adverse effects reported: 3 rabeprazole, 3 lansoprazole, and 2 omeprazole. No biochemistry abnormalities, no significant difference between therapies for changes in gastrin levels or changes in endocrine cells from biopsies	Fair
Chang 1995 Taiwan Single center	*Healing:* *4 weeks:* 95.2% lansoprazole, 92.7% omeprazole *H. Pylori eradication:* *4 weeks:* 78.9% lansoprazole, 82.1% omeprazole	Serum PGA was elevated in both groups (NS), and had returned to baseline at 8 weeks. In both groups, the elevation in PGA was significantly higher in those found to have H. pylori eradication (of those H. pylori positive)	Fair

Evidence Table 7. Randomized controlled trials of duodenal ulcer treatment: Proton pump inhibitor compared with proton pump inhibitor

Author Year Setting	Age, Gender, Race Other Population Characteristics	Intervention	Control	Number
Chang 1995 Taiwan single center (from abstract only – full text not available for this draft)	Not available	Lansoprazole 30 mg once daily x 4 weeks	Omeprazole 20 mg once daily x 4 weeks	111 enrolled (57 lansoprazole, 54 omeprazole)
Dekkers 1999 Belgium, England, Germany Multicenter	Mean age 48 (range 20-77) 65% male 51% smokers 54% alcohol users 83% H. pylori positive	Rabeprazole 20 mg once daily. Duration not clearly stated, but assumed to be 4 weeks based on outcome measure timing	Omeprazole 20 mg a day x 4 weeks (Duration not clearly stated, but assumed to be 4 weeks based on outcome measure timing)	205 enrolled (102 rabeprazole, 103 omeprazole)

Evidence Table 7. Randomized controlled trials of duodenal ulcer treatment: Proton pump inhibitor compared with proton pump inhibitor

Author Year Setting	Outcomes Reported (Results)	Number of Adverse Effects	Quality Rating
Chang 1995 Taiwan single center (from abstract only – full text not available for this draft)	*Healing:* *4 weeks:* (ITT) 89.5% lansoprazole, 83% omeprazole (PP) 96% lansoprazole, 94% omeprazole	Hypergastrinemia in both groups (approximately 1.6 fold increase) Skin rash and constipation occurred in a few cases (groups not specified)	Not assessed
Dekkers 1999 Belgium, England, Germany Multicenter	*Healing rates (ITT):* *2 weeks:* 69% rabeprazole, 61% omeprazole *4 weeks:* 98% rabeprazole, 93% omeprazole *Healing rates (Endo):* *2 weeks:* 69% rabeprazole, 63% omeprazole *4 weeks:* 99% rabeprazole, 96% omeprazole *Pain frequency:* all patients showed improvement (no statistical difference found) *Pain severity:* All patients reported improvement in both daytime and nighttime pain. The only statistically significant difference was found in daytime pain at 4 weeks (92% vs 83% improved, rabeprazole vs omeprazole, p = 0.038). No difference found in the number pain free.	43 patients reported at least on adverse event. (21 rabeprazole, 22 omeprazole). The most common was headache. The mean elevations in serum gastrin levels at 4 weeks were 39.8 pg/ml rabeprazole and 18.9 pg/ml omeprazole.	Fair

Evidence Table 7. Randomized controlled trials of duodenal ulcer treatment: Proton pump inhibitor compared with proton pump inhibitor

Author Year Setting	Age, Gender, Race Other Population Characteristics	Intervention	Control	Number
Dobrilla 1999 Italy Multicenter	Mean age 45 (range 18 - 69) 66% male 52% smokers 34% alcohol use 90% Helicobacter pylori positive	Lansoprazole 30 mg once a day x 4 weeks, then those with healed ulcer randomized to 15 or 30 mg lansoprazole daily x 12 months	Omeprazole 40 mg once a day, then those with healed ulcer switched to omeprazole 20 mg daily x 12 months	251 eligible (167 lansoprazole, 84 omeprazole), unclear number found H. pylori positive who decided not to participate. Maintenance phase: 243 enrolled (164 lansoprazole, 79 omeprazole)

Evidence Table 7. Randomized controlled trials of duodenal ulcer treatment: Proton pump inhibitor compared with proton pump inhibitor

Author Year Setting	Outcomes Reported (Results)	Number of Adverse Effects	Quality Rating
Dobrilla 1999 Italy Multicenter	*Healing:* *4 weeks:* (unclear analysis, only 243 of 251 included) 93.9% lansoprazole, 97.5% omeprazole *PP analysis (# not reported):* 4 weeks: 99% lansoprazole, 100% omeprazole *Symptoms:* *No pain at 4 weeks:* 87.9% lansoprazole, 87.4% omeprazole *Maintenance: (unclear analysis)* *6 months:* 4.5% lansoprazole 15 mg, 0% lansoprazole 30 mg, 6.3% omeprazole relapse *12 months:* 3.3% lansoprazole 15 mg, 0% lansoprazole 30 mg, 3.5% omeprazole *PP analysis:* *6 months:* 0% relapse in all groups *12 months:* 1.9% lansoprazole 15 mg, 0% lansoprazole 30 mg, 3.6% omeprazole relapse *Followup (at 18 months):* 27.3% lansoprazole 15 mg, 20% lansoprazole 30 mg, 26.7% omeprazole relapse	16 during phase I (4 weeks), 10 (6%, lansoprazole), 6 (7.1%, omeprazole) Phase 2 (maintenance): 9 (12.2%, lansoprazole 15 mg), 4 (5.6%, lansoprazole 30 mg), and 8 (11%, omeprazole). The most common adverse event was diarrhea. 8 patients withdrew due to adverse events (3 lansoprazole 15 mg, 2 lansoprazole 30 mg, 3 omeprazole) including diarrhea, rash, gynecomastia, asthenia, precordial pain, fever, and weight gain. No significant changes in laboratory tests were found. Serum gastrin levels were elevated in both groups at 4 weeks (increase of 23.8pg/ml lansoprazole 30 mg, 35.8pg/ml omeprazole; NS), and continued to be elevated at 6 and 12 months of maintenance therapy. The lansoprazole 15 mg group had the least and the lansoprazole 30 mg group had the highest elevation at 6 and 12 months. At 6 months followup all values were returning to baseline.	Fair-poor

Evidence Table 7. Randomized controlled trials of duodenal ulcer treatment: Proton pump inhibitor compared with proton pump inhibitor

Author Year Setting	Age, Gender, Race Other Population Characteristics	Intervention	Control	Number
Ekstrom 1995 Sweden Multicenter	Mean age 55 47% smokers 43% alcohol users 10% NSAID users	Lansoprazole 30 mg once a day x 4 weeks	Omeprazole 20 mg a day x 4 weeks	279 enrolled (143 lansoprazole, 136 omeprazole)
Fanti 2001 Italy Single center	Median age 47 lansoprazole and 48 omeprazole 68% male 56% smokers 54% alcohol users	Lansoprazole 30 mg once a day x 4 weeks Plus clarithromycin 500 and tinidazole 1 gm x 7 days	Omeprazole 20 mg a day x 4 weeks Plus clarithromycin 500 and tinidazole 1 gm x 7 days	43 enrolled (22 lansoprazole and 21 omeprazole)
Ji 2006 Wonju Christian Hospital - South Korea	Mean age 50.7 71.4% male Race NR BMI 22.8 Tobacco use 59.8% Alcohol use 55.4% 75.9% H. pylori positive	Rabeprazole 10 mg once daily in the morning for 6 weeks	Omeprazole 20 mg once daily in the morning for 6 weeks	112 randomized (56 in each group)

Evidence Table 7. Randomized controlled trials of duodenal ulcer treatment: Proton pump inhibitor compared with proton pump inhibitor

Author Year Setting	Outcomes Reported (Results)	Number of Adverse Effects	Quality Rating
Ekstrom 1995 Sweden Multicenter	*Healing rates:* *2 weeks:* *Endo:* 86.2% lansoprazole, 82.1% omeprazole *PPI:* 87.9% lansoprazole, 82.3 omeprazole *4 weeks:* *Endo:* 97.1% lansoprazole, 96.2% omeprazole *PPI:* 97.7% lansoprazole, 96/7% omeprazole *Symptoms:* Most patient's symptoms improved to 'occasional' or 'none' by two weeks, nearly all by 4 weeks in both groups. At 4 weeks the reduction in symptoms favored lansoprazole, p = 0.041 (98% vs 96% with more than occasional symptoms). *Antacids:* no difference found	68 adverse events occurred in 57 patients (23 patients taking lansoprazole, 34 taking omeprazole). No statistically significant difference in the severity was found between the two groups. A statistically significant difference was found in the mean change in ALAT concentration, but the change was minor (0.05 unit increase lansoprazole, 0.03 unit decrease omeprazole).	Fair
Fanti 2001 Italy Single center	*Healing rates:* *8 weeks:* 100% both groups *Symptoms:* "rapid clinical response with disappearance of symptoms in both groups"	"Mild and self-limiting" Total number not reported 1 lansoprazole stomatitis and 1 omeprazole mild diarrhea	Fair
Ji 2006 Wonju Christian Hospital - South Korea	*Remaining ratio of peptic ulcers after 1 week* Rabeprazole 45.5% omeprazole 50.3% p = 0.475 *Healing rates at 6 weeks* (ITT) rabeprazole 80.6% omeprazole 87.0% p = 0.423 *Proportions with daytime symptom resolution at week 6* Rabeprazole 63.6% omeprazole 64.3% p = 0.958 *Proportions with night-time symptom resolution at week 6* Rabeprazole 72.4% omeprazole 73.1% p = 0.956	Three non-serious adverse events in the omeprazole group (2 headache and 1 nausea), and no adverse event in the rabeprazole group	Fair- no methods reported on randomization or blinding and endoscopy was not done on all so analysis is actually a completers analysis for ulcer healing

Evidence Table 7. Randomized controlled trials of duodenal ulcer treatment: Proton pump inhibitor compared with proton pump inhibitor

Author Year Setting	Age, Gender, Race Other Population Characteristics	Intervention	Control	Number
Subei 2007 Multicenter and multinational	Mean age (SD) 40.7 (13.1) 65.2% male 32.4% white, 16.6% black, 5.3% Asian, 45.7% other 100% H. pylori positive	Esomeprazole, 20 mg bid, amoxicillin, 1000 mg bid, and clarithromycin, 500 mg bid (EAC), triple therapy, given for 1 week and followed by 3 weeks of placebo,	Omeprazole 20 mg bid, amoxicillin, 1000 mg bid, and clarithromycin, 500 mg bid (OAC), triple therapy, given for 1 week and followed by 3 weeks of omeprazole, 20 mg od, monotherapy	382 randomized - 374 ITT (186 esomeprazole 188 omeprazole)
Tulassay 2001 Hungary, Poland, Czech Republic Multicenter	Mean age 46 (SD 13) 62% male 100% white 57% smokers all were H. pylori positive	Esomeprazole 20 mg twice daily plus clarithromycin 500 mg and amoxicillin 1 gm twice daily x 1 week, placebo x 3 weeks	Omeprazole 20 mg twice daily mg x 4 weeks plus clarithromycin 500 mg and amoxicillin 1 gm twice daily x 1 week	446 randomized (222 esomeprazole 224 omeprazole)

Evidence Table 7. Randomized controlled trials of duodenal ulcer treatment: Proton pump inhibitor compared with proton pump inhibitor

Author Year Setting	Outcomes Reported (Results)	Number of Adverse Effects	Quality Rating
Subei 2007 Multicenter and multinational	*Healing rates at 4 weeks* (ITT) 73.7% esomeprazole, 76.1% omeprazole 95% CI -11.2% to 6.4% (PP) 76.7% esomeprazole 81.3% omeprazole *Healing rates at 8 weeks* (ITT) 86.6% esomeprazole, 88.3% omeprazole (PP) 92.0% esomeprazole, 94.2% omeprazole *H. pylori eradication at 8 weeks:* (ITT) 74.7% esomeprazole, 78.7% omeprazole 95% CI 72.2–84.3 (PP) 84% esomeprazole, 86.2% omeprazole 95% CI 79.0–91.6	Esomeprazole vs.. Omeprazole Dysgeusia 17 (9.0%) vs.. 23 (11.9%) Diarrhea 16 (8.5%) vs.. 15 (7.8%) Headache 9 (4.8%) vs..14 (7.3%) Abdominal pain 7 (3.7%) vs..4 (2.1%) Nausea 5 (2.6%) vs.. 7 (3.6%)	Fair
Tulassay 2001 Hungary, Poland, Czech Republic Multicenter	*Healing rates:* *4-6 weeks:* (ITT) 91% esomeprazole, 92% omeprazole (PP) 94% esomeprazole, 96% omeprazole *H. pylori eradication:* (ITT) 86% esomeprazole, 88% omeprazole (PP) 89% esomeprazole, 90% omeprazole (NS)	33% of esomeprazole and 29.5% of omeprazole reported at least one adverse event. Most frequent taste perversion, diarrhea, loose stools. 4 discontinued for adverse events (e: 1 for taste perversion/vomiting, o: 1 for rash, 1 allergic reaction, 1 dysmenorrhea). No clinically relevant trends for changes in laboratory safety variables.	Fair

Evidence Table 8. Duodenal ulcer recurrence rates on maintenance therapy

Author, Year Setting	Age, Gender, Race, Other Population Characteristics	Interventions	Control	Number Screened/ Eligible/ Enrolled
Dobrilla 1999 Italy Multicenter	Mean age 45 (range 18 - 69) 66% male 52% smokers 34% alcohol use 90% Helicobacter pylori positive 21% NSAID users; 80% treated with lansoprazole x 8-16 weeks for acute ulcer; 95% H-2 antagonist resistant acute ulcer	Lansoprazole 15 or 30 mg daily x 12 months	Omeprazole 20 mg daily x 12 months	Maintenance phase: 243 enrolled (164 lansoprazole, 79 omeprazole)
Lanza 1997 USA Multicenter	Mean age 43 63% male 76% Caucasian 48% smokers 56% alcohol users	Lansoprazole 15 mg once daily x 12 months or until ulcer recurrence	Placebo once daily x 12 months or until ulcer recurrence	186 enrolled (88 placebo, 92 lansoprazole)

Evidence Table 8. Duodenal ulcer recurrence rates on maintenance therapy

Author, Year Setting	Outcomes Reported	Number of Adverse Effects	Quality Rating	Comments
Dobrilla 1999 Italy Multicenter	*Maintenance: (unclear analysis)* *6 months:* 4.5% lansoprazole 15 mg, 0% lansoprazole 30 mg, 6.3% omeprazole relapse *12 months:* 3.3% lansoprazole 15 mg, 0% lansoprazole 30 mg, 3.5% omeprazole *PP analysis:* *6 months:* 0% relapse in all groups *12 months:* 1.9% lansoprazole 15 mg, 0% lansoprazole 30 mg, 3.6% omeprazole relapse *Followup (at 18 months):* 27.3% lansoprazole 15 mg, 20%lansoprazole 30 mg, 26.7% omeprazole relapse	Serum gastrin levels were elevated in both groups at 4 weeks (increase of 23.8pg/ml lansoprazole 30 mg, 35.8pg/ml omeprazole NS), and continued to be elevated at 6 and 12 months of maintenance therapy. The lansoprazole 15 mg group had the least and the lansoprazole 30 mg group had the highest elevation at 6 and 12 months. At 6 months follow up all values were returning to baseline.	Fair/poor	If assigned to lansoprazole during treatment study, randomized to lansoprazole; if assigned to omeprazole for treatment, omeprazole for maintenance
Lanza 1997 USA Multicenter	*Recurrence:* *12 months:* (ITT) 62% placebo, 27% lansoprazole (Endo) 61% placebo, 26% lansoprazole *Symptoms:* Median time to becoming symptomatic >12 months both groups Asymptomatic during 9-12 months: 75% lansoprazole, 58% placebo *Antacid use (tabs/day):* median 0.08 lansoprazole, 0.23 placebo (P<0.05)	9 adverse events possibly or probably related to study drug. The most common was diarrhea. No significant differences between groups. Serum gastrin levels were significantly higher in lansoprazole group than placebo, median 92pg.ml vs 52 pg/ml (P0.001). Values reached a plateau after one month of treatment and returned to baseline one month after treatment stopped. Gastric biopsies: significant increase in Gastrin cell density in lansoprazole group compared to placebo group (707cells/mm2 vs 556 cells.mm2), no other differences found.	Fair	

Evidence Table 8. Duodenal ulcer recurrence rates on maintenance therapy

Author, Year Setting	Age, Gender, Race, Other Population Characteristics	Interventions	Control	Number Screened/ Eligible/ Enrolled
Kovacs 1999 USA Multicenter	Mean age 57 placebo, 54 lansoprazole 15 mg, 47 lansoprazole 30 mg 88% male 57% smokers 39% alcohol users	Lansoprazole 15 or 30 mg once daily for up to 12 months	Placebo once daily for up to 12 months	19 placebo, 18 lansoprazole 15 mg, 19 lansoprazole 30 mg, other 3 not reported)

Evidence Table 8. Duodenal ulcer recurrence rates on maintenance therapy

Author, Year Setting	Outcomes Reported	Number of Adverse Effects	Quality Rating	Comments
Kovacs 1999 USA Multicenter	*Recurrence:* *1 month:* 27% placebo, 13% lansoprazole 15 mg, 6% lansoprazole 30 mg *12 months:* 30% lansoprazole 15 mg, 15% lansoprazole 30 mg All patients on placebo experienced recurrence or withdrew from study by 6 months. *Symptoms:* *Symptom free at* *12 months:* 82% lansoprazole 15 mg, 76% lansoprazole 30 mg All patients on placebo experienced symptoms, recurrence or withdrew from study by 6 months *Antacid use:* median use (tabs/day): 0.21 placebo, 0 lansoprazole 15 mg, 0.01 lansoprazole 30 mg NS	40 patients reported adverse events (11 placebo, 15 lansoprazole 15 mg, 14 lansoprazole 30 mg). Adverse events possibly or probably related to study drug: 2 placebo, 2 lansoprazole 15 mg, 6 lansoprazole 30 mg. None were severe. Withdrawals due to adverse events: 2 placebo, 3 lansoprazole 15 mg, 1 lansoprazole 30 mg. No significant changes from baseline on labs, physical exam, or ECG. Serum gastrin levels increased significantly in both lansoprazole groups compared to placebo (P<0.001). Elevations occurred within 1 month of starting study. 8 patients (3 lansoprazole 15 mg, 5 lansoprazole 30 mg) had levels >200pg/ml during study. All returned to baseline within 1 month of stopping study drug. Changes in Grimelius-positive	Fair	Prior to enrollment, healing was achieved in all patients with lansoprazole 30 mg.

Evidence Table 8. Duodenal ulcer recurrence rates on maintenance therapy

Author, Year Setting	Age, Gender, Race, Other Population Characteristics	Interventions	Control	Number Screened/ Eligible/ Enrolled
Russo 1997 Italy Multicenter	Mean age 44 68% male 55% smokers (43% >15/day) 32% alcohol users H. pylori positive: 91%	If lansoprazole 30 mg during healing trial: lansoprazole 15 mg or placebo once daily x 12 months or until recurrence	If rabeprazole during healing trial: ranitidine or placebo 150 mg once daily x 12 months or recurrence	Healing: 132 enrolled (68 lansoprazole, 64 ranitidine) Maintenance: 108 enrolled (30 (lansoprazole 30 mg/lansoprazole 15 mg), 28 (lansoprazole 30 mg/placebo), 24 (ranitidine/ranitidine), 26 (ranitidine/placebo)

Evidence Table 8. Duodenal ulcer recurrence rates on maintenance therapy

Author, Year Setting	Outcomes Reported	Number of Adverse Effects	Quality Rating	Comments
Russo 1997 Italy Multicenter	*Recurrence:* (ITT) *3 months:* 7% (lansoprazole/lansoprazole), 14% (lansoprazole/placebo), 8% (ranitidine/ranitidine), 27% (ranitidine/placebo) *6 months:* 17% (lansoprazole/lansoprazole), 32% (lansoprazole/placebo), 33% (ranitidine/ranitidine), 46% (ranitidine/placebo) *9 months:* 23% (lansoprazole/lansoprazole), 36% (lansoprazole/placebo), 38% (ranitidine/ranitidine), 50% (ranitidine/placebo) *12 months:* 23% (lansoprazole/lansoprazole), 39% (lansoprazole/placebo), 46% (ranitidine/ranitidine), 50% (ranitidine/placebo) (P=0.081 (l/l) vs (ranitidine/ranitidine) *Symptoms:* results not reported	*Maintenance* : Reported as 3% (lansoprazole/lansoprazole), 18% (lansoprazole/placebo), 0% (ranitidine/ranitidine); (ranitidine/placebo) not reported	*Healing:* Good/Fair *Maintenance:* Fair/Poor	Healing: lansoprazole 30 mg or ranitidine. baseline information on maintenance phase participants not reported. Attrition/compliance for maintenance not reported. Results for symptoms during healing phase not reported.

Evidence Table 8. Duodenal ulcer recurrence rates on maintenance therapy

Author, Year Setting	Age, Gender, Race, Other Population Characteristics	Interventions	Control	Number Screened/ Eligible/ Enrolled
Graham 1992 USA Multicenter	Mean age 48 omeprazole, 50 ranitidine, 47 placebo % male: 75% omeprazole, 67% ranitidine, 69% placebo Mean index ulcer size cimetidine: 0.9 omeprazole, 0.8 ranitidine (P<0.01); placebo not reported other variables reported as NS	None	None	240 enrolled (80% of omeprazole, 63% of ranitidine and 27% of placebo patients eligible enrolled)

Evidence Table 8. Duodenal ulcer recurrence rates on maintenance therapy

Author, Year Setting	Outcomes Reported	Number of Adverse Effects	Quality Rating	Comments
Graham 1992 USA Multicenter	Life table analysis relapse rates: 78% omeprazole, 60% (ranitidine), 50% placebo (NS)	None reported	Fair	Followup study of omeprazole 20 mg vs ranitidine or omeprazole 20 mg vs placebo

Evidence Table 9. Randomized controlled trials of gastric ulcer treatment

Author Year Setting	Age, Gender, Race, Other Population Character-istics	Interventions	Control	Number Screened/ Eligible/ Enrolled	Outcomes Reported (Results)
Dekkers 1998 Belgium, England, Germany, Iceland, Ireland, Netherlands, Poland, Spain, Sweden Multicenter	Mean age 55 57% male 52% smokers 57% H. Pylori positive 24% antacid use 96% had >/= 0.5cm ulcer	Rabeprazole 20mg once daily. Duration not clearly stated, but assumed to be 6 weeks based on outcome measure timing.	20 mg of omeprazole	227 enrolled	***Healing rates by ITT:*** *3 weeks:* 58% (r), 61% (o) *6 weeks:* 91% (r and o) *3 weeks:* 58% (r), 63% (o) *6 weeks:* 93% (r and o) *3 weeks:* 60% (r), 59% (o) *6 weeks:* 52% (r), 44% (o) ***Pain severity:*** no pain *3 weeks:* 68% (r), 61% (o) *6 weeks:* 84% (r), 68% (o) Overall well-being at 3 and 6 weeks comparable for both groups
Ando, 2005	Mean age 51 77% male 83% H. pylori positive 16% poor metabolizers	Rabeprazole 10 mg once daily 8 weeks	20 mg of omeprazole	80 enrolled	***Healing rates by ITT:*** *2 weeks:* 85.9%% (r), 76.5% (o) 8 *weeks:* 88.9% (r) 87.8% (o)

Evidence Table 9. Randomized controlled trials of gastric ulcer treatment

Author Year Setting	Number of Adverse Effects	Quality Rating
Dekkers 1998 Belgium, England, Germany, Iceland, Ireland, Netherlands, Poland, Spain, Sweden Multicenter	60 patients reported at least one adverse event. (25 (r), 35 (o)). The most common was headache. Slightly elevated creatine phosphokinase at 6 weeks was found in 6 (o) patients. The mean elevations in serum gastrin levels at 6 weeks were 12.7 pg/ml (r)and 10.0 pg/ml (o).	Fair
Ando, 2005	8 adverse events reported in 5 patients R: abdominal pain, nausea, headaches O: diarrhea, abdominal pain, nausea flatulence, headache	Fair

Evidence Table 9. Randomized controlled trials of gastric ulcer treatment

Author Year Setting	Age, Gender, Race, Other Population Character-istics	Interventions	Control	Number Screened/ Eligible/ Enrolled	Outcomes Reported (Results)
Florent 1994 France	Mean age 56 64% male 49% smokers	Lansoprazole 30 mg once daily 4 to 8 weeks	20 mg of omeprazole	126 enrolled	***Healing Rates by PP:*** *4 weeks:* 82% (l), 68% (o) *8 weeks:* 93% (l), 82% (o) ***Pain Relief:*** *Daytime:* 86% (l), 60% (o) *Nocturnal pain:* 100% (l), 70% (o) *Time to daytime pain relief:* 6.6 d (l), 11 d (o)
DiMario 1994 Italy Multicenter Maintenance study	Mean age 47.9 (23-75) 71% male 13% gastric ulcers, 79% duodenal ulcers, 8% both gastric and duodenal ulcer All ulcers resistant to H2 blocker therapy (unhealed after 8 weeks of therapy)	Omeprazole 20 or 40 mg daily for 4 weeks, extended to 8 weeks if necessary. After healing: omeprazole 20 mg daily (30 patients) omeprazole 20 mg every other day (29 patients) omeprazole 20 mg twice weekly (29 patients)	Ranitidine 150 mg (12 patients only)	# screened, eligible not reported, 102 enrolled	***Recurrence (6 months) by ITT:*** 23.3% Omeprazole 20 mg daily (p <0.02 vs ranitidine) 19.4% Omeprazole 20 mg every other day (p<0.005 vs ranitidine) 58.6% Omeprazole 20 mg twice weekly 66.7% Ranitidine 150 mg

Evidence Table 9. Randomized controlled trials of gastric ulcer treatment

Author Year Setting	Number of Adverse Effects	Quality Rating
Florent 1994 France	23 adverse events were reported (8 (l), 15 (o)). The most common adverse event with L was diarrhea, and was headache and diarrhea with O.	Poor- open label, high drop-out rate, differential loss to followup, not ITT
DiMario 1994 Italy Multicenter Maintenance study	No side effects were reported during the maintenance treatment period; 1 patient reported headache in healing period (at oemp 40 mg daily; resolved). 11 patients dropped out (27% in omep 20 mg every day group, 0 in omep every other day, 73% in omep 20 mg twice weekly)	Poor- open, differential loss to followup

Evidence Table 9. Randomized controlled trials of gastric ulcer treatment

Author Year Setting	Age, Gender, Race, Other Population Character-istics	Interventions	Control	Number Screened/ Eligible/ Enrolled	Outcomes Reported (Results)
Kovacs 1999 USA Multicenter Maintenance Study	Mean age 58 (pl), 57 (l15), 58 (l30) 85% male 67% smokers 47% alcohol users 96% acute disease H-2 RA resistant	Lansoprazole 15 or 30mg once daily for up to 12 months (if recurrence occurred, treated with open-label lansoprazole 30mg daily x 8 weeks, then resumed originally assigned maintenance treatment).	Placebo once daily for up to 12 months (if recurrence occurred, treated with open-label lansoprazole 30mg daily x 8 weeks, then resumed originally assigned maintenance treatment).	52 patients eligible, 49 enrolled	***Recurrence:*** median < 2 months (pl), > 12 months (l groups) *At 1 month:* 40% (pl), 0% (l15), 7% (l30) *12 months:* 0% (pl), 17% (l15), 7% (l30) (P<0.001 (l groups vs (pl)) ***Symptoms:*** Of those asymptomatic at baseline 0%? (pl), 100% (l15), 59% (l30) no symptoms at 12 months *Antacid use:* (tabs/day) Median 0.38 (pl), 0.02 (l15), 0.01 (l30)

Evidence Table 9. Randomized controlled trials of gastric ulcer treatment

Author Year Setting	Number of Adverse Effects	Quality Rating
Kovacs 1999 USA Multicenter Maintenance Study	39 patients reported 1 or > adverse events reported (13 (pl), 14 (l15), 12 (l30), NS. The most common adverse events that were possibly or probably related to study drug were diarrhea (0%(pl), 0% (l15), 13.3% (l30) and constipation (12.5% (pl), 5.3% (l15), 0% (l30)). 7 patients withdrew due to adverse events (4 (pl), 1 (l15), 2 (l30)). No clinically significant lab changes, vital signs, or ECG seen. Serum Gastrin Significantly (P</= 0.003) greater changes from baseline seen in (l) groups vs (pl) 4 (l15), and 15 (l30) fasting levels > 200 pg/ml during study Increases occurred within 1 month of starting (l) and returned to baseline within 1 month of stopping drug Gastric Mucosal Biopsy Increases in Grimelius positive cell density in the corpus (from baseline) 121 cells/mm2 (pl), 146 cells/mm2 (l15), 176 cells/mm2 (l30) (P=0.001 vs (pl)). No other cell changes seen.	Fair

Evidence Table 9. Randomized controlled trials of gastric ulcer treatment

Author Year Setting	Age, Gender, Race, Other Population Character-istics	Interventions	Control	Number Screened/ Eligible/ Enrolled	Outcomes Reported (Results)
Cooperative Study 1990 UK Multicenter	Mean age: 57 (o), 61 (ran) 54% male 65% smokers 74% alcohol users	Omeprazole 40mg once daily x 2 to 8 weeks	Ranitidine 150mg twice daily x 2 to 8 weeks	46 enrolled (21 (o), 25 (ran)) 27 enrolled in followup study (12 (o), 15 (ran))	***Healing (PP):*** *4 weeks:* 81% (o), 58% (ran)(NS) *8 weeks:* 93% (o), 87% (ran)(NS) ***Pain free (baseline not reported)*** *2 weeks:* 53% (o), 42% (ran)(NS) *4 weeks:* 73% (o), 38% (ran)(NS) *8 weeks:* 50% (o), 44% (ran) (NS) Nighttime pain at 2 weeks (o) < (r), data not reported, (P<0.03) Daytime pain (o) < (ran)in weeks 3 and 4 by diary card, data not reported, (P<0.03) ***Recurrence:*** *6 months:* 42% (o), 67% (ran)(NS)

Evidence Table 9. Randomized controlled trials of gastric ulcer treatment

Author Year Setting	Number of Adverse Effects	Quality Rating
Cooperative Study 1990 UK Multicenter	1 death judged to be unrelated to study. 9 patients reported adverse events (5 (o), 4 (ran)). The most common were GI symptoms.	Poor

Evidence Table 9. Randomized controlled trials of gastric ulcer treatment

Author Year Setting	Age, Gender, Race, Other Population Character-istics	Interventions	Control	Number Screened/ Eligible/ Enrolled	Outcomes Reported (Results)
Walan 1989 13 countries (primarily European plus Australia and Canada), 45 centers	Mean age 55 (o20), 57 (o40), 58 (ran) % smokers 61% (o20), 60% (o40), 56% (ran) % alcohol users 60% (o20), 57% (o40), 50% (ran) NSAID use 11% (o20), 12% (o40), 11% (ran)	Omeprazole 20mg or 40mg once daily x 4 to 8 weeks	Ranitidine 150mg twice daily x 4 to 8 weeks	602 enrolled (436 gastric ulcers, 166 prepyloric ulcers)	***Healing:*** ***Gastric + prepyloric (PP analysis):*** *4 weeks:* 69% (o20), 80% (o40), 59% (ran) *8 weeks:* 89% (o20), 96% (o40), 85% (ran) ***ITT analysis reported as 'similar'*** *Prepyloric only:* (PP analysis) *2 weeks:* 33% (o20), 42% (o40), 27% (ran)(NS) ***NSAID users (PP analysis)*** *4 weeks:* 61% (o20), 81% (o40), 32% (ran) *8 weeks:* 82% (o20), 95% (o40), 53% (ran) ***Symptoms:*** *None at 2 weeks:* 62% (o20), 69% (o20), 55% (ran)((o40) vs (ran)P= 0.02) *Followup Study:* *Healing maintained at 6 months:* 59% (O40 and O20), 53% (ran) (P=0.03 (o40) vs (ran)) *No symptoms 'during followup':* 52% (O40 and O20), 48% (ran)(P=0.02 (o40) vs (ran))
Rossini 1989 Italy Single center	Data not reported – stated to be similar	Omeprazole 20mg or 40mg once daily x 4 to 8 weeks	Ranitidine 150mg twice daily x 4 to 8 weeks	18 enrolled (number per group not stated)	***Healing*** *4 weeks:* 78% (o), 50% (ran) *8 weeks:* 100% (o), 87% (ran) Pain disappeared almost completely in both groups by two weeks

Evidence Table 9. Randomized controlled trials of gastric ulcer treatment

Author Year Setting	Number of Adverse Effects	Quality Rating
Walan 1989 13 countries (primarily European plus Australia and Canada), 45 centers	106 patients reported adverse events (34 (o20), 32 (o40), 40 (ran)). The most common were GI symptoms, similar in all groups. Numbers withdrawn or lost to follow up: 21 (o20), 19 (o40), 22 (ran) 3 patients died during study (all on (o40)) of causes shown to be unrelated to study drug, 2 patients withdrawn due to abnormal labs also shown to be unrelated to study drugs ((1 (o40), 1 (ran)).	Good/Fair Comment: Patients enrolled in followup study not well described, attrition not described.
Rossini 1989 Italy Single center	None reported in either group	Fair/poor

Evidence Table 9. Randomized controlled trials of gastric ulcer treatment

Author Year Setting	Age, Gender, Race, Other Population Character-istics	Interventions	Control	Number Screened/ Eligible/ Enrolled	Outcomes Reported (Results)
Classen 1985 Germany Multicenter	Data not reported – stated to be similar	Omeprazole 20mg once daily x 4 to 6 weeks	Ranitidine 150mg twice daily x 4 to 6 weeks	184 enrolled	***Healing (PP analysis only):*** *2 weeks:* 43% (o), 45% (ran) (NS) *4 weeks:* 81% (o), 80% (ran) (NS) *6 weeks:* 95% (o), 90% (ran) NS ***Symptoms:*** "equally good with either drug"
Bardhan 1994 United Kingdom and Sweden Multicenter	Mean ages 60 (l60), 59(l30), 57(r) 57% males 65% UK 35% Sweden 52% smokers 60% alcohol use 11% NSAID use	Lansoprazole 30mg or 60mg once a day x 4 to 8 weeks	Ranitidine 300mg every night x 4 to 8 weeks	250 enrolled	***Healing rates:*** *4 weeks:* *of those with endoscopy:* 78% (120), 84% (160), 61% (ran) ***ITT:*** 72% (l30), 73% (l60), 52% (ran) ***PP:*** 80% (l30), 78% (l60) 57% (ran) *8 weeks:* *of those w/endoscopy:* 99% (l30), 97% (l60), 91% (ran) ***ITT:*** not reported ***PP:*** 98% (l30), 100% (l60), 90% (ran) *Symptoms:* proportion symptom free at 4 weeks: *Pain:* 75% (l30), 72% (l60), 65% (ran) *Nausea:* 88% (l30), 89% (l60), 76% (ran) *Vomiting:* 100% (l30), 87% (l60), 89% (ran)

Evidence Table 9. Randomized controlled trials of gastric ulcer treatment

Author Year Setting	Number of Adverse Effects	Quality Rating
Classen 1985 Germany Multicenter	Not reported	Poor Comment: This appears to be a report in English of two trials previously published in German, therefore the quality of the trials may be higher than appears from this paper.
Bardhan 1994 United Kingdom and Sweden Multicenter	69 patients experienced 91 adverse events, 26% (l30), 27% (l60), 30% (ran). The most common thought to be possibly or probably related to study drug were diarrhea and headache.	Fair

Evidence Table 9. Randomized controlled trials of gastric ulcer treatment

Author Year Setting	Age, Gender, Race, Other Population Character-istics	Interventions	Control	Number Screened/ Eligible/ Enrolled	Outcomes Reported (Results)
Michel 1994 France Multicenter	Mean age 52 (l), 56 (ran) 69% male 38% smokers 52% alcohol users 42% NSAID users mean ulcer size 12mm (l), 11mm (ran)	Lansoprazole 30mg once daily x 4 to 8 weeks	Ranitidine 150mg twice daily x 4 to 8 weeks	158 enrolled	***Healing:*** *4 weeks:* ITT 68% (l), 56% (ran)NS PP: 80% (l), 62% (ran)(p<0.05) *8 weeks:* ITT 81% (l), 76% (ran)(NS) PP: 100% (l), 87% (ran)(P<0.05) *No epigastric pain:* (at baseline 26% (l), 22% (ran)) *4 weeks:* 73% (l), 72% (ran)(NS) *8 weeks:* 95% (l), 92% (ran)(NS)
Capurso 1995 Italy Multicenter	Data not reported – stated to be similar	Lansoprazole 30mg once daily x 2 to 8 weeks	Ranitidine 300mg once daily x 1 x 2 to 8 weeks	74 enrolled (34 (l), 35 (o), 5 not reported)	***Healing rates:*** *2 weeks:* 41.4% (l), 26.5% (ran) *4 weeks:* 79.3% (l), 61.8% (ran) *8 weeks:* 96.6% (l), 94.1% (ran) ***Pain:*** at 2 weeks no significant difference between groups 64% pain free

Evidence Table 9. Randomized controlled trials of gastric ulcer treatment

Author Year Setting	Number of Adverse Effects	Quality Rating
Michel 1994 France Multicenter	38 patients reported adverse events. 4 withdrawn due to serious adverse events all (r)group). 3 of these were deaths (1 acute heart failure, 2 acute respiratory distress), the forth withdrawn due to femur fracture resulting from hypotension. GI symptoms (diarrhea, constipation were the most common adverse effects reported in both groups).	Fair Comment: Numbers of subjects in PP analysis do not add up. Table 2 shows 3 patients withdrawn due to adverse events, but text reports 4. Table 2 reports 16 lost from (l) (79 - 16 = 63) but only 62 included in PP analysis. Likewise, number analyzed at 4 weeks on (ran)reported as 68, but 12 reported lost (79 - 12 = 67)
Capurso 1995 Italy Multicenter	8 adverse effects reported: 3 (ran), 3 (l), and 2 (o) No biochemistry abnormalities, no significant difference between therapies for changes in gastrin levels or changes in endocrine cells from biopsies	Fair

Evidence Table 9. Randomized controlled trials of gastric ulcer treatment

Author Year Setting	Age, Gender, Race, Other Population Character-istics	Interventions	Control	Number Screened/ Eligible/ Enrolled	Outcomes Reported (Results)
Hotz 1995 Germany Multicenter (28)	Median age 55 (p), 57 (r) 60% male 45% smokers 9.7% everyday alcohol users mean ulcer diameter 10.9 (p), 11.2 (r)	Pantoprazole 40mg once daily x 2, 4 or 8 weeks depending on healing. (2:1 randomization p:r)	Ranitidine 300mg every night x 2, 4 or 8 weeks depending on healing	248 enrolled.	***Healing:*** *2 weeks:* ITT: 33% (p), 17% (ran) (P<0.01) PP: 37% (p), 19% (ran) (P<0.01) *4 weeks:* ITT 77% (p), 52% (ran) (P<0.001) PP: 87% (p), 57% (ran) (P<0.001) *8 weeks:* ITT 86% (p), 72% (ran) (P<0.01) PP: 97% (p), 80% (ran) (P<0.001) No pain:(13% (p), 8% (ran) at baseline) (PP) *2 weeks: 7* 2% (p), 68% (ran) (NS) Based on diary card, no difference between groups in time to becoming pain free Other GI symptoms also improved in both groups
Tsuji 1995	Mean age 64 81% male 50% H. pylori positive	Lansoprazole 30mg once x 4 to 8 weeks	Famotidine 40mg x 16 4 to 8 weeks		***Healing:*** *4 weeks:* 71% (l), 29% (f) *8 weeks:* 83% (l), 57% (f) Symptoms not reported

Evidence Table 9. Randomized controlled trials of gastric ulcer treatment

Author Year Setting	Number of Adverse Effects	Quality Rating
Hotz 1995 Germany Multicenter (28)	26 patients reported adverse events (15 (p), 11 (ran). The most frequent was diarrhea (3) and headache (2) on (pl), and sleep disorder (2) on (ran). 4 (p) and 3 (ran) withdrew due to adverse events, 1 (r) patient had elevated serum transaminase levels, otherwise lab values were normal. Median change in serum gastrin levels at 8 weeks: 30pg.ml (pl), 12pg/ml (ran), median values at all time points were higher in the (p) group.	Good/Fair
Tsuji 1995	None	Fair

Evidence Table 9. Randomized controlled trials of gastric ulcer treatment

Author Year Setting	Age, Gender, Race, Other Population Character-istics	Interventions	Control	Number Screened/ Eligible/ Enrolled	Outcomes Reported (Results)
Okai 1995	Mean age 54 (range 36-86) (l30) 59 (range 39-80) (f) 75% male 71% smokers 38% ulcer size >15mm	Lansoprazole 30mg once daily x 2 to 8 weeks	Famotidine 40mg once daily x 2 to 8 weeks	24	***Healing:*** *4 weeks:* 50% (l), 0% (f) *8 weeks:* 54.5% (l), 18.2% (f) (from Kovacs, 1998) **Symptoms:** Pain free at week 1:80% (l), 60% f) (NS)
Bate 1989 UK and Republic of Ireland Multicenter	Mean age 57 47% male 59% smokers 3% ulcer size >10mm	Omeprazole 20mg once daily x 4 to 8 weeks	Cimetidine 800mg x 4 to 8 weeks	197 enrolled (105 (o), 92 (c))	***Healing (ITT):*** *4 weeks:* 73% (o), 58% (c) (P<0.05) *8 weeks:* 84% (o), 75 (c) (NS) ***Symptoms*** ***Pain free*** *4 weeks:* 81% (o), 60% (c) (P<0.01) *8 weeks:* "difference no longer significant" *4 weeks* (but not at 8 weeks) Daytime pain and heartburn less in (o) (P<0.05) data not reported. No difference in nocturnal pain or nausea Diary cards: 2 weeks: (o) better than (c) for daytime pain (P<0.01), nighttime pain (P<0.05) and antacid use (P<0.0001)

Evidence Table 9. Randomized controlled trials of gastric ulcer treatment

Author Year Setting	Number of Adverse Effects	Quality Rating
Okai 1995	None	Fair
Bate 1989 UK and Republic of Ireland Multicenter	32 patients reported adverse events (19% (o), 15% (c)). 2 were serious, but considered unrelated to study. 7 (4 (o),3 (c)) withdrew due to adverse events (2 in (o) were due to lack of efficacy). The most common adverse events were GI and CNS system related in both groups	Fair/Poor

Evidence Table 9. Randomized controlled trials of gastric ulcer treatment

Author Year Setting	Age, Gender, Race, Other Population Character-istics	Interventions	Control	Number Screened/ Eligible/ Enrolled	Outcomes Reported (Results)
Lauritsen 1988 Denmark Multicenter	Mean age 57 45% male 74% smokers mean ulcer 9.7, 10.7 mm	Omeprazole 30mg once daily x 6 weeks	Cimetidine 1000mg x 6 weeks	179 eligible, 176 enrolled (3 chose not to participate)	***Healing:*** *2 weeks:* ITT: 54% (o), 39% (c) PP: 55% (o), 42% (c) *4 weeks:* ITT 81% (o), 73% (c) PP: 85% (o), 77% (c) *6 weeks:* ITT 86% (o), 78% (c) PP: 89% (o), 86% (c) ***No pain:*** (24% (o), 14% (c) at baseline) *2 weeks:* 48% (o), 29% (c) *4 weeks:* 57% (o), 47% (c) *6 weeks:* 62% (o), 58% (c) Number of hours of pain at 6 weeks: 7.5 (o), 10.5 (c)

Evidence Table 9. Randomized controlled trials of gastric ulcer treatment

Author Year Setting	Number of Adverse Effects	Quality Rating
Lauritsen 1988 Denmark Multicenter	12 reports of adverse events. (o): one each: headache, fatigue, transient diarrhea, gastroenteritis, muscle pain. (c): one each of headache, dry mouth, 2 each of dizziness, impotence	Fair

Evidence Table 9. Randomized controlled trials of gastric ulcer treatment

Author Year Setting	Age, Gender, Race, Other Population Character-istics	Interventions	Control	Number Screened/ Eligible/ Enrolled	Outcomes Reported (Results)
Danish Omeprazole Study Group 1989	Median age 60 (range 52-71) (o) 61 (range 50-72) (c) 48% male 69% smokers	Omeprazole 30mg x 2 to 6 weeks	Cimetidine 1000mg x 2 to 6 weeks	161 enrolled 146 evaluated	***Healing:*** *2 weeks:* 41% (o), 41% (c) *4 weeks:* 77% (o), 58% (c) *6 weeks:* 88% (o), 82% (c) ***Symptoms*** ***Mean days with pain:*** *2 weeks:* 5 (o), 5.5 (c) *4 weeks:* 4.3 (o), 3.8(c) *6 weeks:* 2.4 (o), 2.4(c) (all NS) 6-month followup (untreated) no difference in relapse rate (Endo):17% (o), 19% (c)
Aoyama 1995	Data not reported – stated to be similar	Lansoprazole 30mg x 2 to 8 weeks	Cimetidine 800mg x 2 to 8 weeks	107 enrolled 84 evaluated	***Healing:*** *2 weeks: 14% (l), 6% (c)* *4 weeks:71% (l), 47% (c)* *6 weeks:* 94% (l), 75% (c)

Evidence Table 9. Randomized controlled trials of gastric ulcer treatment

Author Year Setting	Number of Adverse Effects	Quality Rating
Danish Omeprazole Study Group 1989	3 withdrawals due to adverse effects in (c) group due to 'other diseases' and urticarial reaction. 19 other adverse events reported. (o) group: allergic edema, itching, diarrhea (2 cases), tremor, polyuria, shoulder pain, and pulmonary edema.. (c) group: itching, diarrhea, constipation (2), dizziness (2), fatigue (2), insomnia, and back pain (2).	Poor
Aoyama 1995	Not reported.	Poor

Evidence Table 10. Randomized controlled trials of nonsteroidal anti-inflammatory drug-induced ulcer treatment

Author Year Setting Purpose	Age, Gender, Race, Other population characteristics	Interventions	Control	Number Screened/ Eligible/ Enrolled
Hawkey 1998 International (14 countries including USA) Treatment or prevention	Mean age 58 (range 20 to 85) 38% male 23% smokers 39% H. pylori positive 8% history of bleeding ulcer 41% gastric ulcer 38% rheumatoid arthritis	20 mg or 40 mg of omeprazole once daily (duration not clearly stated, assumed to be 8 weeks)	200 mcg of misoprostol four times daily	935 enrolled

Evidence Table 10. Randomized controlled trials of nonsteroidal anti-inflammatory drug-induced ulcer treatment

Author Year Setting Purpose	Outcomes reported (results)	Number of adverse effects	Quality rating
Hawkey 1998 International (14 countries including USA) Treatment or prevention	***Treatment Success at 8 weeks:*** 76% (o20), 75% (o40), 71% (m) (NS) ***ITT analysis:*** 75% (o20), 75% (40), 71% (m) ***GU only:*** 87% (o20), 80% (o40), 73% (m) (P=0.004 (o20) vs (m); 0.14 (o40) vs (m) ***GU and DU:*** 85% (o20), 79% (o40), 74% (m) ***DU only:*** 93% (o20), 89% (o40), 77% (m) ***Erosions only:*** 77% (o20), 79% (o40), 87% (m) ***H. pylori positive:*** 83% (o20), 83% (o40), 69% (m) ***H. pylori negative:*** 73% (o20), 70% (o40), 74% (m) ***Symptoms:*** Reduction in mod-severe dyspepsia at 4 weeks 34% (o20), 39% (o40), 27% (m) Proportion of days with abdominal pain 43% (o20), 43% (o40), 50% (m) Proportion of days with heartburn 16% (o20), 14% (o40), 29% (m) QOL (completed by 68% (o20), 66% (o40), 62% (m)) Gastrointestinal Symptom Rating Scale at 8 weeks change in total score-0.47 (o20), -0.36 (o40), -0.20 (m) change in reflux score: -0.82 (o20), -0.75 (o40), -0.33(m) change in diarrhea score: -0.24 (o20), -0.06 (o40), +0.22 (m) Nottingham Health Profile change in sleep score: -3.1 (o20), -8.6 (m), (o40 not reported)	470 patients reported adverse events (48% (o20), 46% (o40), 59% (m) Most common reported was diarrhea (4.5% (o20), 5.3% (o40), 11.4 % (m)	Fair Comment: Patients without healing at eight weeks received open treatment with 40 mg of omeprazole daily for a further four to eight weeks.

Evidence Table 10. Randomized controlled trials of nonsteroidal anti-inflammatory drug-induced ulcer treatment

Author Year Setting Purpose	Age, Gender, Race, Other population characteristics	Interventions	Control	Number Screened/ Eligible/ Enrolled
Yeomans 1998 International (15 countries) Treatment or prevention	Mean age 57 33% male 10% history of bleeding ulcer 39% gastric ulcer 46% H. pylori positive 44% rheumatoid arthritis	20 mg or 40 mg of omeprazole once daily for four or eight weeks	150 mg of ranitidine twice daily for four or eight weeks	541 enrolled

Evidence Table 10. Randomized controlled trials of nonsteroidal anti-inflammatory drug-induced ulcer treatment

Author Year Setting Purpose	Outcomes reported (results)	Number of adverse effects	Quality rating
Yeomans 1998 International (15 countries) Treatment or prevention	***Treatment Success at 8 weeks:*** 80% (o20), 79% (o40), 63% (ran) ***GU only:*** 84% (o20), 87% (o40), 64% (ran) ***DU only:*** 92% (o20), 88% (o40), 81 (ran) ***Erosions only:*** 89% (o20), 86% (o40), 77% (ran) ***H. pylori positive*** *:* 83% (o20), 82% (o40), 72% (m) *H. pylori negative:* 75% (o20), 71% (o40), 55% (m) ***Symptoms:*** *reduction of 'moderate to severe' category at 4 weeks:* 46% (o20), 38% (ran) (o40 not reported)	190 moderate to severe adverse events were reported (30% (o20), 38% (o40), 40% (r) GI effects (diarrhea, nausea, constipation, and flatulence) were the most common reported Discontinuation of therapy due to either and adverse event or lack of efficacy (not reported separately): 2.8% (o20), 3.2% (o40), 8.5% (ran)	Fair

Evidence Table 10. Randomized controlled trials of nonsteroidal anti-inflammatory drug-induced ulcer treatment

Author Year Setting Purpose	Age, Gender, Race, Other population characteristics	Interventions	Control	Number Screened/ Eligible/ Enrolled
Agrawal 2000 USA and Canada, multicenter healing only	Mean age 60 35% male 90% white 21% smokers 31% alcohol users 29% H. pylori positive	Lansoprazole, 15 or 30 mg once daily for 8 weeks	Ranitidine 150 mg twice daily for 8 weeks	Endoscopy was performed on 669 patients, 353 met inclusion criteria.

Evidence Table 10. Randomized controlled trials of nonsteroidal anti-inflammatory drug-induced ulcer treatment

Author Year Setting Purpose	Outcomes reported (results)	Number of adverse effects	Quality rating
Agrawal 2000 USA and Canada, multicenter healing only	***Healing: Gastric Ulcer*** *4 weeks:* 47% (l15), 57% (l30), 30% (ran) *8 weeks:* 69% (l15), 73% (l30), 53% (ran) ***GU and DU 8 weeks** :* 93% (l15), 81% (l30), 88% (ran) ***GU or erosions 8 weeks:*** 85% (l15), 100% (l30), 86% (l30) ***H. pylori positive: 8 weeks:*** 67% (l15), 82% (l30), 60% (ran) ***H. pylori negative** :* 70% (l15), 69% (l30), 51% (ran) ***Symptoms:*** *4 weeks:* no daytime pain 66% (l15), 64% (l30), 60% (ran) no nighttime pain 67% (l15), 69% (l30), 64% (ran) % days antacids used 67% (l15), 70% (l30), 62% (ran) *8 weeks:* no daytime pain 70% (l15), 66% (l30), 63% (ran) no nighttime pain 71% (l15), 71% (l30), 69% (ran) % days antacids used 69% (l15), 71% (l30), 64% (ran)	33 patients reported an adverse event, 15 patients stopped taking study medication because of adverse events (5 (l15), 4 (l30), 6 (ran)). The most commonly reported treatment-related event was diarrhea.	Good/Fair

Evidence Table 11. Randomized controlled trials of proton pump inhibitors for prevention of nonsteroidal anti-inflammatory drug-induced ulcer

Author Year	Population setting	Diagnosis	Eligibility criteria	Interventions	Control
Lai et al. 2002	123 patients, double blind, ITT. Hong Kong, mean age 70 (range 18-80), female 28%, race NR. 245 screened, 171 eligible by H. pylori, 127 treated, 4 H. pylori uneradicated.	History of cerebrovascular accident (52%) or heart disease (48%) - endo revealed gastric (74%), duodenal (21%) or gastroduodenal (5%) ulcer.	- History of stroke or ischemic heart disease requiring long-term aspirin therapy; - Ulcer developed after at least one month low-dose aspirin therapy; - H. pylori infection; - Ulcer and H. pylori successfully eradicated during initial healing phase of study; - No esophagitis, history of ulcer surgery, comcomitant treatment with NSAIDs, corticosteroids or anticoagulant agents, active cancer, or allergic to study drugs.	30 mg (l) + 100 mg aspirin bid for median 12 months	Matching placebo + 100 mg aspirin bid
Graham, 2002	US and Canada Multicenter Mean age 60 65% female 90% white, 6% black, 4% other.	No H. pylori; reason for long-term NSAID use not reported, previous GI disease: 59% reflux esophagitis, 50% duodenal ulcer, 99% gastric ulcer.	Age 18 or older, h/o endoscopically-documented gastric ulcer with or without coexisting duodenal ulcer or GI bleeding, and treatment with stable, full therapeutic doses of an NSAID (except nabumetone or aspirin >1300 mg/day) for at least the previous month.	lansoprazole 15 or 30 mg for 12 weeks	misoprostol 200 mcg qid for 12 weeks

Evidence Table 11. Randomized controlled trials of proton pump inhibitors for prevention of nonsteroidal anti-inflammatory drug-induced ulcer

Author Year	Other Medications	Definition of Treatment Failure/Success	Outcomes Reported (Results)	Adverse Effects	Quality Rating
Lai et al. 2002	Antacid permitted, advised to avoid other NSAIDs if possible	Primary endpoint: recurrence of ulcer complications (bleeding, outlet obstruction, perforation). Secondary endpoint: recurrence of ulcer.	Clinical Bleeding: (l) = 0, (pl) = 8 (p<.01) Ulcer recurrence: (l) = 1, (pl) = 9 (p=.008) H. pylori recurrence: (l) = 0, (pl) = 4 (p<.05)	Death: (l) = 1, (pl) = 0 Other adverse effects NR.	
Graham, 2002	40% ibuprofen, 35% naproxen, 32% diclofenac, 22% aspirin or aspirin combinations, 17% piroxicam, 34% other NSAIDS	Occurrence of gastric ulcer (definition of gastric ulcer not specified), included analysis with withdrawals considered treatment failures (having a gastric ulcer).	*Treatment success:* *Free of gastric ulcer by week 12 (per protocol):* *(pl)* :51% (m): 93% (l15): 80% (l30): 82% *Treatment success:* *Results when withdrawals classified as treatment failures:* *(pl)* :34% (m): 67% (l15): 69% (l30): 68%	Withdrawals due to adverse events: (pl) 6.7%, (m) 10.4%, (l15) 2.9%, (l30) 7.5%; Higher percentage of treatment related adverse events in misoprostol group (31% (m), 10% (pl), 7% (l15), 16% in (l30); most common diarrhea. One upper GI tract hemorrhage (l15).	Fair: randomization and allocation method not reported.

Evidence Table 11. Randomized controlled trials of proton pump inhibitors for prevention of nonsteroidal anti-inflammatory drug-induced ulcer

Author Year	Population setting	Diagnosis	Eligibility criteria	Interventions	Control
Bianchi Porro 2000	Italy Single center Mean age 59.9 (range 22-80) 83% female ethnicity not given	63% rheumatoid arthritis 38% osteoarthritis.	Over age 18, with rheumatoid arthritis or osteoarthritis, treated with effective and constant doses of NSAIDs (diclofenac, ketoprofen, indomethacin) for at least 8 weeks prior to start of study. Lanza endoscopic grade 0,1, or 2.	pantoprazole 40 mg	placebo
Labenz et al. 2002	2264 patients screened, 832 randomized, 660 analyzed - in 3 countries in central Europe, double blind, not ITT. Mean age: 55 Male: 38%	Systemic inflammatory disease (24%), noninflammatory disease (73%), mild dyspepsia (42%), Lanza score "0" on study entry (stomach 68%; duodenum 89%).	Age >18 years with inflammatory disease of musculoskeletal system requiring NSAID treatment >5 weeks, and H. pylori positive. Excluded for ulcer or history of ulcer, clotting disorders, prior regular use of NSAIDS (except aspirin <100 mg/day), antibiotics, PPIs, misoprostol, or bismuth salts within 4 weeks; regular use of H2R antagonists, prokinetics or sucralfate; systemic corticosteroids, known or suspected intolerance to study drug, severe concomitant diseases; previous gastric surgery; pregnancy or nursing; and dyspepsia therapy.	OAC-O = omeprazole 40 mg + amoxicillin 2 g +clarithro-mycin 1000 mg for 1 week, then 20 mg ome for 4 weeks. O-O = 20 mg ome for 5 weeks.	OAC-P = OAC for 1 week, then placebo for 4 weeks. P-P = placebo for 5 weeks.

Evidence Table 11. Randomized controlled trials of proton pump inhibitors for prevention of nonsteroidal anti-inflammatory drug-induced ulcer

Author Year	Other Medications	Definition of Treatment Failure/Success	Outcomes Reported (Results)	Adverse Effects	Quality Rating
Bianchi Porro 2000	37% diclofenac, 34% ketoprofen, 35% indomethacin.	Occurrence of gastric or duodenal ulcers (grade 4, Lanza classification) after 4 and 12 weeks, or patients who discontinued the study due to lack of efficacy leading to discontinuation of the study medication, an adverse event which was assessed by the study investigator as possibly or definitely related to the study medication.	*Ulcer status assigned (treatment failure):* (p)*:* 13 with endoscopically-proven peptic ulcer, 3 due to lack of efficacy, 2 adverse events (pl)*:* 9 with endoscopically-proven peptic ulcer (1 with both gastric and duodenal ulcer), 1 lack of efficacy , 2 adverse events. *Endoscopically proven duodenal and/or gastric ulcers:* (p)*:* 13 (pl)*:* 9	4.3% (p) (m) unrelated to treatment, vomiting possibly related, diarrhea definitely related), 5.9% (pl) (diarrhea possibly related, asthenia definitely related), all withdrew for adverse events.	Fair/Good: concealment of allocation not reported
Labenz et al. 2002	NSAID treatment: diclofenac 100-150 mg, and could add tramadol 200 mg. Dyspeptic therapy with an antacid.	Primary endpoint: endoscopically proved peptic ulcer. Secondary endpoints: dyspeptic complaints, signs of gastrointestinal bleeding.	OAC-O vs. O-O vs. OAC-P vs. P-P Developed peptic ulcers - Total: 2/173 (1.2%) vs. 0/155 vs. 2/161 (1.2%) vs. 10/171 (5.8%) - Duodenal: 0/173 vs. 0/155 vs. 2/161(1.2%) vs. 7/171(4.1%) - Gastric: 2/173 (1.2%)vs. 0/155 vs. 0/161 vs. 3/171 (1.8%) (Bonferroni p-value significant for all ome groups vs. pla) Dyspepsia developed requiring therapy: 10.4% vs. 12.3% vs. 10.6% vs. 19.9% (All treatment groups significantly different from pla only group - p-value NR) Negative H. pylori status: 85.3% vs. 21.9% vs. 81.3% vs. 11.8%	201 of 660 patients reported 302 adverse events (no details reported): OAC-O 31% O-O 16% OAC-P 26% P-P 26% Diarrhea more frequent in antibiotic groups: OAC-O 8.8% O-O 3.0% OAC-P 8.4% P-P 3.3%	

Evidence Table 11. Randomized controlled trials of proton pump inhibitors for prevention of nonsteroidal anti-inflammatory drug-induced ulcer

Author Year	Population setting	Diagnosis	Eligibility criteria	Interventions	Control
Hawkey, 1998	93 centers in 14 countries mean age 58 (range 20-85) 64% female ethnicity not given	38% rheumatoid arthritis, 47% osteoarthritis, 13% other, 2% combinations.39% gastric ulcer with or without erosions, 20% duodenal ulcer with or without erosions, 4% gastric and duodenal ulcer with or without erosions, 36% erosions only.	Patients who successfully healed during treatment phase of study. Age 18 to 85, with any condition requiring continuous treatment with oral or rectal NSAIDS above a predetermined minimal dose (no maximal dose). Minimal (and mean) daily oral doses: 50 mg (129 mg) diclofenac, 100 mg (137 mg) ketoprofen, 500 mg (844 mg) naproxen. By endoscopy, any or all of the following: ulcer, defined as a mucosal break at least 3 mm in diameter with definite depth in the stomach, duodenum, or both, more than 10 gastric erosions, and more than 10 duodenal erosions.	omeprazole 20 mg	misoprostol 200 mcg bid or placebo
Yeomans 1998	73 centers in 15 countries; mean age 56 (range 20-80); 69% female; ethnicity not given	44% rheumatoid arthritis, 32% osteoarthritis, 6% psoriatic arthritis, 5% anklyosing spondylitis	Age 18 to 85, with any condition requiring continuous therapy with NSAIDs above specified therapeutic doses (no maximal dose),and not more than 10 mg prednisolone or equivalent per day. By endoscopy, any or all of the following: ulcers 3 mm of more in diameter, more than 10 erosions in stomach, more than 10 erosions in the duodenum. (Lanza scale)	omeprazole 20 mg	ranitidine 150 mg bid

Evidence Table 11. Randomized controlled trials of proton pump inhibitors for prevention of nonsteroidal anti-inflammatory drug-induced ulcer

Author Year	Other Medications	Definition of Treatment Failure/Success	Outcomes Reported (Results)	Adverse Effects	Quality Rating
Hawkey, 1998	At baseline (all patients):most common diclofenac (23%), naproxen (22%), ketoprofen (16%).	Development of any of the following: an ulcer, more than 10 gastric erosions, more than 10 duodenal erosions, at least moderate symptoms of dyspepsia, or adverse events resulting in the discontinuation of treatment.	*In remission at 6 months:* (o20):61%(m): 48%(pl): 27%p = 0.001 for (o20) vs (m) *Gastric ulcers at relapse:(* o20):13%(m):10%(pl):32% *Duodenal ulcers at relapse:(* o20): 3%(m):10%(pl):12%	Withdrawals due to adverse events: (o20): 3.9%, (m): 7.7%, (pl): 1.9%; most common diarrhea (7.6% (o20), 8.4% (m), 4.5% (pl), abdominal pain (5.1% (o20), 4.7% (m), 5.8% (pl). One perforated duodenal ulcer after 31 days of (pl).	Fair: randomization and allocation method not reported, not intention-to-treat.
Yeomans 1998	Not reported for maintenance phase. Most common at baseline (including healing phase) diclofenac (29%), indomethacin (23%), naproxen (16%)	Remission defined as absence of a relapse of lesions, dyspeptic symptoms, and adverse events leading to the discontinuation of treatment.	*In remission at 6 months:* (o20): 72%(r): 59%p = 0.004	Any adverse event: (o20): 64%, (r): 58%; withdrawals due to adverse events: 6.1% (o20), 3.2% (ran). Most common arthritis, rheumatoid arthritis, vomiting (2.9% (o20), 2.3% (ran)), abdominal pain (2.9% (o)o, 1.9% (ran)), diarrhea (3.3% (o20), 1.4% (ran)). One bleeding duodenal ulcer after 10 days of (o20).	Fair: randomization and allocation method not reported, not intention-to-treat.

Evidence Table 11. Randomized controlled trials of proton pump inhibitors for prevention of nonsteroidal anti-inflammatory drug-induced ulcer

Author Year	Population setting	Diagnosis	Eligibility criteria	Interventions	Control
Stupnicki et al. 2003	515 patients, multiple European countries Multicenter, double-blind 73% female median age 64 (range 31-93) ethnicity not reported	55% erosions at entrance exam; 45% 1-5 erosions; 32% H. pylori positive; 41% osteoarthritis, 30% rheumatoid arthritis, 2% spondylitis, 7% spondylosis, 19% multiple disease.	Outpatients aged 55 or older receiving or planned to receive continuous NSAID therapy for rheumatoid arthritis, osteoarthritis, arthrosis, spondylosis, or spondylitis, and who experienced gastrointestinal symptoms of at most moderate intensity. No signs of reflux esophagitis (endoscopically-proven). At least one of the following criteria: history of endoscopically proven peptic ulcer (including bleeding and/or perforation) within the last 5 years, or history of repeated gastrointestinal symptoms within the last year, or intake of more than one NSAID (the second NSAID could be dosed below the minimal dose), or regular intake of corticosteroids as concomitant medication, or regular intake of anticoagulants as concomitant medication, or NSAID treatment since maximally 4 weeks, or change of the NSAID drug substance since maximally 4 weeks.	pantoprazole 20 mg for 6 months	misoprostol 400 mcg for 6 months

Evidence Table 11. Randomized controlled trials of proton pump inhibitors for prevention of nonsteroidal anti-inflammatory drug-induced ulcer

Author Year	Other Medications	Definition of Treatment Failure/Success	Outcomes Reported (Results)	Adverse Effects	Quality Rating
Stupnicki et al. 2003	17% more than one NSAID, 17% corticosteroids, 2% anticoagulants	Therapeutic failure: more than 10 erosions/petechiae in the stomach/duodenum, peptic ulcer, reflux esophagitis, discontinuation of study due to an adverse event assessed as "likely" or "definitely" related to the study medication.; discontinuation of study due to severe gastrointestinal symptoms Endoscopic failure: more than 10 erosions/petechiae in the stomach/duodenum, peptic ulcer, reflux esophagitis Symptomatic failure: severe gastrointestinal symptoms	*In remission at 3 months:* 76% pantoprazole vs 63% misoprostol In remission at 6 months: 67% pantoprazole vs 52% misoprostol *Remission rates for therapeutic failure (pantoprazole vs misoprostol)* 3 months: 93% vs 79% (p<0.001) 6 months: 89% vs 70% (p<0.001) *Remission rates for endoscopic failure (pantoprazole vs misoprostol)* 3 months: 98% vs 95% (NS) 6 months: 95% vs 86% (p=0.005) *Remission rates for symptomatic failure (pantoprazole vs misoprostol)* 3 months: 99% vs 92% (p=0.005) 6 months: 99% vs 92% (p=0.002)	Withdrawals due to adverse events: 5% pantoprazole vs 13% misoprostol (events assessed by investigator as likely or definitely related to study drug) 3 deaths in pantoprazole group; all assessed as not related to study drug. serious adverse events: 18 pantoprazole vs 16 misoprostol patients serious adverse events classified as at least 'likely' related to study drug: 0 pantoprazole vs 2 misoprostol (hypertensive crisis and diarrhea)	Fair: Allocation concealment method not reported, baseline characteristics given for ITT population only.

Evidence Table 12. Adverse effects in short term randomized controlled trials: Proton pump inhibitor compared with proton pump inhibitor

Author Year Setting	Disease	Intervention	Control	Number Enrolled	Number withdrawn due to adverse events
Johnson et al. 2002 UK & Ireland Multicenter Crossover	Chronic PPI treatment for benign ulcers or GERD	omeprazole 20 mg/day	rabeprazole 20 mg/day	240	30/240 (12.5%)
Beker 1995 European Multicenter	Duodenal ulcer	pantoprazole 40mg	omeprazole 20mg	270 enrolled (135 each group)	0.74% (p)2.9% (o)
Capruso 1995 Italy Multicenter	Duodenal ulcer	lansoprazole 30mg	omeprazole 20mg	107 enrolled, (52 (l), 55(r))	Not reported
Chang 1995 Taiwan Single center	Duodenal ulcer	lansoprazole 30mg once a day x 4 weeks	omeprazole 20mg a day x 4 weeks	111 enrolled (57 (l), 54 (o)	Not stated in abstract

Evidence Table 12. Adverse effects in short term randomized controlled trials: Proton pump inhibitor compared with proton pump inhibitor

Author Year Setting	Adverse effects
Johnson et al. 2002 UK & Ireland Multicenter Crossover	(o) = 115 (51%) reported 114 mild, 117 moderate, and 30 serious treatment-emergent AEs. (r) = 120 (52.6%) reported 97 mild, 118 moderate, and 28 severe treatment-emergent AEs. No significant differences in AEs between groups. No difference in general preference for (o) or (r). - More patients prefer (r) for "absence of side effects" (p=.047), among those with any preference (46%). - More patients prefer (r) for "unexpected positive side effects" (p=.019), among those with any preference (28%). - More patients prefer tablet form of (r) as "easy to swallow" (p=.0001), among those with any preference (52%). - More patients prefer capsule form of (o) as "easy to pick up and hold" (p=.0003), among those with any preference (47%).
Beker 1995 European Multicenter	21 patients reported adverse events (10, 7% (p), 11, 8% (o)), with a total of 23 events reported. Diarrhea was the most common adverse event reported. 5 were considered serious (1 (p), GI hemorrhage and 4 (o), angina pectoris, hypertension, vertigo and abdominal pain. These patients were withdrawn from study. Serum gastrin levels rose in both groups at both 2 and 4 weeks, the change was statistically significant within but not between groups.
Capruso 1995 Italy Multicenter	8 adverse effects reported: 3 (r), 3 (l), and 2 (o). No significant difference between therapies for changes in gastrin levels or changes in endocrine cells from biopsies
Chang 1995 Taiwan Single center	Hypergastrinemia with both agents. A few occurrences of reversible skin rash and constipation.

Evidence Table 12. Adverse effects in short term randomized controlled trials: Proton pump inhibitor compared with proton pump inhibitor

Author Year Setting	Disease	Intervention	Control	Number Enrolled	Number withdrawn due to adverse events
Chang 1995 Taiwan Single-center	Duodenal ulcer	lansoprazole 30mg	omeprazole 20mg	83 enrolled (42 (l), 41 (o))	None reported
Dekkers 1999 European Multicenter	Duodenal ulcer	rabeprazole 20mg	omeprazole 20mg	205 enrolled (102 (r), 103 (o))	1.9% (o) 0% (r)
Dobrilla 1999 Italy Multicenter	Duodenal ulcer	lansoprazole 30mg, then those with healed ulcer randomized to 15 or 30mg lansoprazole x 12 months	omeprazole 40mg, then those with healed ulcer switched to omeprazole 20mg x 12 months	251 eligible (167 (l), 84 (o)) Maintenance phase: 243 enrolled (164 (l), 79(o))	Treatment:2.3% (o), 9% (l)Maintenance:4% (l15), 2.8% (l30), 1.4% (o)
Ekstrom 1995 Sweden Multicenter	Duodenal ulcer	lansoprazole 30mg	omeprazole 20mg	279 enrolled (143 (l), 136 (o))	Not reported
Fanti 2001 Italy Single center	Duodenal ulcer and H. pylori	lansoprazole 30mg once a day x 4 weeks Plus clarithromycin 500 and tinidazole 1gm x 7 days	omeprazole 20mg a day x 4 weeks Plus clarithromycin 500 and tinidazole 1gm x 7 days	43 enrolled (22 (l) and 21 (o))	None
Kovacs 1999 USA Multicenter	Duodenal ulcer maintenance	lansoprazole 15 or 30mg once daily for up to 12 months	placebo once daily for up to 12 months	56 enrolled19 (pl),18 (l15), 19 (l30)	21.5%(pl)17% (l15)5.3% (l30)

Evidence Table 12. Adverse effects in short term randomized controlled trials: Proton pump inhibitor compared with proton pump inhibitor

Author Year Setting	Adverse effects
Chang 1995 Taiwan Single-center	Serum PGA was elevated in both groups (NS), and had returned to baseline at 8 weeks. In both groups, the elevation in PGA was significantly higher in those found to have H. pylori eradication
Dekkers 1999 European Multicenter	43 patients reported at least one adverse event. (21 (r), 22 (o)). The most common was headache. 2 (o) withdrew due to adverse events (evaluated as unrelated to study)The mean elevations in serum gastrin levels at 4 weeks were 39.8 pg/ml (r) and 18.9 pg/ml (o).
Dobrilla 1999 Italy Multicenter	16 during phase I (healing): 10 (6%, l), 6 (7.1%, o) 21 during Phase 2 (maintenance): 9 (12.2%, l15), 4 (5.6%, l30), and 8 (11%, o) Most common adverse event was diarrhea. 8 patients withdrew due to adverse events (3 (l15), 2 (l30), 3 (o))Serum gastrin levels were elevated in both groups at 4 weeks (increase of 23.8pg/ml (l30), 35.8pg/ml (o) NS), and continued to be elevated at 6 and 12 months of maintenance therapy. The (l15) had the least and the (l30) had the highest elevation at 6 and 12 months. At 6 months all values were returning to baseline.
Ekstrom 1995 Sweden Multicenter	68 adverse events occurred in 57 patients (23 (l), 34 (o)) (NS). A statistically significant difference was found in the mean change in ALT concentration, but the change was minor (0.05 unit increase (l), 0.03 unit decrease (o).
Fanti 2001 Italy Single center	“Mild and self-limiting” Total number not reported.1 (l) stomatitis and 1 (o) mild diarrhea
Kovacs 1999 USA Multicenter	40 patients reported adverse events (11 (pl), 15 (l15), 14 (l30)). Adverse events possibly or probably related to study drug: 2 (pl), 2 (l15), 6 (l30). None were severe. Serum gastrin levels increased significantly in both (l) groups compared to (pl) (P<0.001). Elevations occurred within 1 month of starting study. 8 patients (3(l15), 5 (l30)) had levels >200pg/ml during study. All returned to baseline within 1 month of stopping study drug.

Evidence Table 12. Adverse effects in short term randomized controlled trials: Proton pump inhibitor compared with proton pump inhibitor

Author Year Setting	Disease	Intervention	Control	Number Enrolled	Number withdrawn due to adverse events
Lanza 1997 USA Multicenter	Duodenal ulcer maintenance	lansoprazole 15mg once daily x 12 months or until ulcer recurrence	placebo once daily x 12 months or until ulcer recurrence	186 enrolled 88 (pl), 92 (l))	4.5% (pl) 2.2% (l)
Russo 1997 Italy Multicenter	Duodenal ulcer maintenance	If (l30) during healing trial: Lansoprazole 15 mg or Placebo once daily x 12 months or until recurrence	If (r) during healing trial: Ranitidine or placebo 150mg once daily x 12 months or recurrence	108 enrolled 30 (l30/l15)28 (l30/p), 24 (ran/ran),26 (ran/p)	Not reported
Dekkers 1998 European Multicenter	Gastric ulcer	rabeprazole 20mg	omeprazole 20 mg	227 enrolled	Not reported
Adachi, 2003	GERD	rabeprazole 20 mg	omeprazole 20 mg or lansoprazole 30 mg	85	Not reported
Bardhan, 2001	GERD	pantoprazole 20 mg	omeprazole 20 mg	328	Not reported

Evidence Table 12. Adverse effects in short term randomized controlled trials: Proton pump inhibitor compared with proton pump inhibitor

Author Year Setting	Adverse effects
Lanza 1997 USA Multicenter	9 adverse events possibly or probably related to study drug. The most common was diarrhea. No significant differences between groups. Serum gastrin levels were significantly higher in (l) group than (pl), median 92pg.ml vs 52 pg/ml (P0.001). Values reached a plateau after one month of treatment and returned to baseline one month after treatment stopped. Gastric biopsies: significant increase in Gastrin cell density in (l) group compared to (pl) group (707cells/mm2 vs 556 cells.mm2), no other differences found.
Russo 1997 Italy Multicenter	Maintenance: 3% (l/l), 18% (l/pl), 0% (ran/ran). (ran/pl) not reported.
Dekkers 1998 European Multicenter	60 patients reported at least one adverse event. (25 (r), 35 (o)). The most common was headache. No difference by sex, age, race.Slightly elevated creatine phosphokinase at 6 weeks was found in 6 (o) patients. The mean elevations in serum gastrin levels at 6 weeks were 12.7 pg/ml (r) and 10.0 pg/ml (o).
Adachi, 2003	Not reported
Bardhan, 2001	57% of pantoprazole vs 50% omeprazole experienced adverse events. Severe in 10% pantoprazole and 13% omeprazole patients. Most events judged unrelated or unlikely to be related to the study drug. Most common adverse events (pantoprazole vs omeprazole): nausea (8% vs 7%), diarrhea (5% vs 6%), and headache (6% vs 3%).

Evidence Table 12. Adverse effects in short term randomized controlled trials: Proton pump inhibitor compared with proton pump inhibitor

Author Year Setting	Disease	Intervention	Control	Number Enrolled	Number withdrawn due to adverse events
Castell 1996 US Multicenter	GERD	lansoprazole 15 mg or 30 mg	omeprazole 20 mg	1070	(o20): 2% (l30): 1.7% (l15): 0.9%
Chen et al 2005	GERD	esomeprazole 40mg	omeprazole 20 mg	48 (25 esomeprazole, 23 omeprazole)	Not reported
Corinaldesi 1995 European Multicenter	GERD	pantoprazole 40 mg	omeprazole 20 mg	241	(p40): 0.8% (o20): 1.7%
Dekkers 1999 European Multicenter	GERD	rabeprazole 20 mg	omeprazole 20 mg	202	(r20): 1% (o20): 0
Delchier 2000 European Multicenter	GERD	rabeprazole 20 mg or ransoprazole 10 mg	omeprazole 20 mg	300	(r10): 5% (r20): 5% (o20): 2%
Dupas 2001 France Multicenter	GERD	pantoprazole 40 mg	lansoprazole 30 mg	461	(p40): 1.3% (l30): 2.5%

Evidence Table 12. Adverse effects in short term randomized controlled trials: Proton pump inhibitor compared with proton pump inhibitor

Author Year Setting	Adverse effects
Castell 1996 US Multicenter	Any adverse event:(l15) 44.5%, (l30) 55.7%, (o20) 53.4%. Most commonly reported events headache, diarrhea, nausea. More patients in (ll5) reported nausea (p<0.05). 6 severe events possibly or probably related to medication (4 in (o20) , 1 in (l15), 1 in (l30).
Chen et al 2005	No treatment related serious AEs reported. 7 esomeprazole and 6 omeprazole patients reported non-serious AEs, most commonly constipation (6.3% of all patients) and dry skin (8.3% of all patients.)
Corinaldesi 1995 European Multicenter	Adverse events reported by 15% of patients in (p40), 12% in (o20). Diarrhea, abdominal pain, hyperlipemia and constipation most frequently reported in (p40) , diarrhea most frequently (o20).
Dekkers 1999 European Multicenter	32% (r20) and 28% (o20) reported at least one adverse event. Headache, diarrhea, flatulence most common. Flatulence more common (o20) gr (4% vs 0%). One serious event (r20) (t wave changes).
Delchier 2000 European Multicenter	21% (r20), 26% (r10), and 23% (o20) reported at least one event. Abdominal pain, pharyngitis, bronchitis, headache, diarrhea most common. Four serious events, none related to medication. At week 4, incidences of elevated serum gastrin levels 16% (r20), 27% (r10), 20% (o20) (NS)
Dupas 2001 France Multicenter	Adverse events reported in 28% in p40 group, 17% in l30. Most common headache, diarrhea, elevation of hepatic enzymes, abdominal pain, skin disorders. 11 serious events (5 (p40) 6 (l30)).

Evidence Table 12. Adverse effects in short term randomized controlled trials: Proton pump inhibitor compared with proton pump inhibitor

Author Year Setting	Disease	Intervention	Control	Number Enrolled	Number withdrawn due to adverse events
Fennerty, 2005	GERD	esomeprazole 40 mg	lansoprazole 30 mg	1001	5/499 (1%) esomeprazole vs 9/472 (2%) lansoprazole.
Gillessen, 2004	GERD	pantoprazole 40 mg	esomeprazole 40 mg	227	6 patients overall, not reported by group.
Hatlebakk 1993 Norway/ Sweden Multicenter	GERD	lansoprazole 30 mg	omeprazole 20 mg	229	(o20): 0.9%(l30):0
Holtmann, 2002	GERD	rabeprazole 20 mg	omeprazole 20 mg	251	4/125 (3%) rabeprazole vs 2/126 (2%) omeprazole
Howden et al. 2002	GERD	lansoprazole 30 mg	esomeprazole 40 mg	284	2/143 (1.4%) lansoprazole vs 5/141 (3.5%) esomeprazole

Evidence Table 12. Adverse effects in short term randomized controlled trials: Proton pump inhibitor compared with proton pump inhibitor

Author Year Setting	Adverse effects
Fennerty, 2005	33.1% esomeprazole vs 36.9% lansoprazole reported an adverse event. Most were mild or moderate. No treatment-related adverse events reported. Most common adverse events (occurring in >2% of patients) were Barrett's esophagus, gastritis, diarrhea, and headache. Most common adverse event leading to study withdrawal was abdominal pain (2 in each group).
Gillessen, 2004	23/113 (20%) pantoprazole vs 20/114 (18%) esomeprazole had an adverse event. None judged definitely related to study medication, 9% pantoprazole, 28% esomeprazole likely related. Two serious adverse events in one patient in pantoprazole group (icterus and malignant hepatic neoplasm (not related to medication). Most frequent adverse event was dizziness (2%).
Hatlebakk 1993 Norway/ Sweden Multicenter	32.8% (l30), 29.2% (o20) reported adverse event, One (o20) withdrawn for severe diarrhea. Headache in 4 pts (o20), none (l30).2 severe events (l30) (1 pharyngitis, 1 nausea, vomiting).
Holtmann, 2002	About 25% of patients in both groups experienced any adverse event. Most frequent were gastrointestinal system in 25 patients (10%) and nervous in 11 patients (4.4%). Seven GI events judged drug-related. Most events mild to moderate; 10 of 90 rated as "severe." No obvious differences in tolerability between treatments (data not reported by group).
Howden et al. 2002	Lansoprazole vs esomeprazole: Incidence of all adverse events 46.2% vs 52.5% Of these, 16.1% vs 19.1% considered "possibly", "probably", or "definitely" treatment-related. Most frequently reported treatment-related effects: diarrhea (5% vs 5%), headache (2% vs 5%), eructation (5% vs 2%), abdominal pain (2% vs 4%), flatulence (1% vs 4%), nausea (2% vs 2%). Most events mild to moderate. Esomeprazole one severe case each of eructation, dizziness, and paresthesia; lansoprazole one severe case each of abdominal pain, diarrhea, eructation, rectal disorder, and somnolence.

Evidence Table 12. Adverse effects in short term randomized controlled trials: Proton pump inhibitor compared with proton pump inhibitor

Author Year Setting	Disease	Intervention	Control	Number Enrolled	Number withdrawn due to adverse events
Kahrilas 2000 US Multicenter	GERD	esomeprazole 40 mg or 20 mg	omeprazole 20 mg	1960	(e40): 2% (e20): 2.6% (o20): 2%
Kao, 2003	GERD	esomeprazole 40 mg	omeprazole 20 mg	100	Not reported
Korner et al. 2003	GERD	pantoprazole 40 mg	omeprazole MUPS 40 mg	669	4/337 (1%) pantoprazole, 7/332 (2%) omeprazole MUPS
Labenz 2005 Multinational, Multicenter	GERD	esomeprazole 40 mg	pantoprazole 40 mg	3151	33/1562 (2.1%) esomeprazole vs 29/1589 (1.8%) pantoprazole

Evidence Table 12. Adverse effects in short term randomized controlled trials: Proton pump inhibitor compared with proton pump inhibitor

Author Year Setting	Adverse effects
Kahrilas 2000 US Multicenter	Total or per group not reported. Most common: headache 8.6% (e40), 8.7% (e20), 6.9% (o20) abdominal pain 3.7% (e40), 3.7% (e20), 4.2% (o20) diarrhea (4.6% (e40), 4.7% (e20), 3.9% (o20) flatulence (1.8% (e40), 3.5% (e20), 4.0% (o20) gastritis 2.5% (e40), 3.5% (e20), 2.5% (o20) nausea 3.8% (e40), 2.9% (e20), 3.1% (o20). No differences observed according to gender, age, or race. No serious drug-related events reported.
Kao, 2003	Not reported
Korner et al. 2003	Pantoprazole vs omeprazole 6% vs 7%, mostly mild or moderate. 2.1% vs 1.2% severe. Most frequently reported adverse event headache for pantoprazole (1%), diarrhea for omeprazole (2%).
Labenz 2005 Multinational, Multicenter	Serious adverse events: 1.5% esomeprazole vs 1.3% pantoprazole. Most commonly reported in esomeprazole group: nausea (6 patients), dizziness (5 patients); In pantoprazole group: headache (5 patients), diarrhea (4 patients).

Evidence Table 12. Adverse effects in short term randomized controlled trials: Proton pump inhibitor compared with proton pump inhibitor

Author Year Setting	Disease	Intervention	Control	Number Enrolled	Number withdrawn due to adverse events
Mee 1996 UK and Ireland Multicenter	GERD	lansoprazole 30 mg	omeprazole 20 mg	604	Not reported
Mulder 1996 Netherlands Multicenter	GERD	lansoprazole 30 mg	omeprazole 40 mg	211	None
Richter 2001 US Multicenter	GERD	esomeprazole 40 mg	omeprazole 20 mg	2425	1% in each group
Richter 2001b	GERD	lansoprazole 30 mg	omeprazole 20 mg	3410	40/1754 (2%) lansoprazole 33/1756 (2%) omeprazole.
Scholten et al. 2003	GERD	pantoprazole 40 mg	esomeprazole 40 mg	217	3 (groups not reported)
Caos et al, 2005	GERD relapse prevention	rabeprazole 10 or 20 mg	placebo	497	rabeprazole 10 mg 11% (n=18) rabeprazole 20 mg 12% (n=19) placebo 4% (n=7)
Richter et al 2004	GERD relapse prevention	pantoprazole 20 or 40 mg	ranitidine 150 mg	349	Not reported

Evidence Table 12. Adverse effects in short term randomized controlled trials: Proton pump inhibitor compared with proton pump inhibitor

Author Year Setting	Adverse effects
Mee 1996 UK and Ireland Multicenter	51% of all patients had at least one event, not broken down by treatment group. Most frequent events: headache (12% (l30), 11% (o20) diarrhea (9.4% (l30), 8% (o20) nausea (4.3% (l30), 4.7% (o20). 2 serious events (o20) (esophageal cancer (pre-existing) and vasovagal syncope and loose stools)
Mulder 1996 Netherlands Multicenter	19% (l), 21% (o) No difference in change in gastrin levels between groups. No other events reported.
Richter 2001 US Multicenter	At least one adverse event reported in 32.2% in(e40), 34.3% in (o20). Most common: headache 6.2% (e40), 5.8% (o20) diarrhea 3.9% (e40), 4.7% (o20) nausea 3.0% (e40), 3.0% (o20) abdominal pain 2.6% (e40) 2.7% (o20) < 1% in each group had a serious event (0 considered treatment related)
Richter 2001b	44% in both groups, most mild or moderate. Lansoprazole vs omeprazole significant differences in incidence of diarrhea (10% vs 8%), increased appetite (0.3% vs 0%), melena (0.1% vs 0.7%), asthma (0.4% vs 0%).
Scholten et al. 2003	14% of patients reported an adverse event, most assessed as "not related" to the study drug. Three patients in each group had an event assessed as "likely" or "definitely" related to study drug. No significant differences between groups in frequency or type of adverse events.
Caos et al, 2005	8%(n=42) of patients experienced AE judged to be drug related, only serious AE occurred in placebo patient. Most common non-serious AEs 20 mg rabeprazole v 10 mg rabeprazole v placebo respectively were: rhinitis (33%, 32%, 12%); diarrhea (28%, 27%, 12%); flu syndrome (23%, 20%, 8%); headache (21%, 25%, 12%); pharyngitis (21% for both treatment groups, 9% for placebo); surgical procedure (20%, 19%, 4%); back pain (19% for both treatment groups, 8% for placebo); abdominal pain (17%,19%,6%); nausea (18%,16%, and 8%) and pain (18%,25%,6%). p ≤0.018 v placebo for all comparisons.
Richter et al 2004	Specific serious AEs not reported, however 6.5% or pantoprazole patients and 3.4% of ranitidine patients are reported as having serious AEs. Other AEs were headache (13% of pantoprazole and 6% of ranitidine patients; p=0.093) Pantoprazole patients also reported as having abdominal pain (11%) diarrhea (10%) and infection (11%.)

Evidence Table 12. Adverse effects in short term randomized controlled trials: Proton pump inhibitor compared with proton pump inhibitor

Author Year Setting	Disease	Intervention	Control	Number Enrolled	Number withdrawn due to adverse events
Tsai et al, 2004	GERD relapse prevention	Acute phase: esomeprazole 20 mg/day Maintenance phase: esomeprazole 20 mg on-demand	lansoprazole 15 mg/day	Acute phase: 774 Maintenance phase: 622	Acute phase: 18 Maintenance phase:40 - 10 (3%) esomeprazole and 30 (10%) lansoprazole
Armstrong et al., 2004	NERD	esomeprazole 20 mg or 40 mg	omeprazole 20 mg	2645 (in 3 trials)	Not reported
Fock et al., 2005	NERD	rabeprazole 10 mg	esomeprazole 20 mg	134	1 esomeprazole (headache)
Monikes et al., 2005	NERD	pantoprazole 20 mg	esomeprazole 20 mg	529	Not reported
Peura et al., 2004	NERD	lansoprazole 15 mg, or 30mg	placebo	921	Not reported
van Zyl et al., 2004	NERD	pantoprazole 20 mg	ranitidine 300 mg	338	9/338 (2.6%)

Evidence Table 12. Adverse effects in short term randomized controlled trials: Proton pump inhibitor compared with proton pump inhibitor

Author Year Setting	Adverse effects
Tsai et al, 2004	17 patients reported 24 serious AEs, including 3 AEs during the acute phase. During the maintenance phase, 9 esomeprazole patients reported 14 serious AEs and 5 lansoprazole patients reported 6 serious AEs. All but one AE (anaphylaxis in a lansoprazole patient) considered unrelated. AEs reported (serious and non-serious) by 42% of acute phase patients and 71% of maintenance phase patients, most commonly headache and diarrhea. Lansoprazole patients were more likely to discontinue due to AEs than esomeprazole patients (7% v 2%, p=0.0028) and more likely to have diarrhea (14% v 5%, p<0.001)
Armstrong et al., 2004	Not reported: "Overall, esomeprazole 40 mg and 20 mg, and omeprazole 20 mg were well-tolerated and the proportions of patients experiencing AEs were similar between treatment groups during the study period."
Fock et al., 2005	AEs considered related to study drug: 22% rabeprazole, 18.2% esomeprazole (NS). Elevation in ALT: 1 rabeprazole, 4 esomeprazole Increase in AST: 1 rabeprazole, 2 esomeprazole (not clinically significant)
Monikes et al., 2005	Not reported: "Both therapies were well tolerated and safe."
Peura et al., 2004	Diarrhea: 6 lansoprazole 15mg, 8 lansoprazole 30mg, 4 placebo Headache: 5 lansoprazole 15mg, 7 lansoprazole 30mg, 9 placebo
van Zyl et al., 2004	Diarrhea: 1 pantoprazole, Constipation: 1 pantoprazole, 1 ranitidine Urticaria: 1 pantoprazole, 1 ranitidine Nausea: 2 ranitidine, Pruritus: 1 ranitidine Vertigo: 1 ranitidine Lower abdominal pain: 1 ranitidine

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Intervention treatment strategy (drug, dose, duration)	Comparison treatment strategy (drug, dose, duration)	Baseline demographics (age, sex, race/ethnicity)	Eligibility criteria
Bytzer 2004 International (Europe) and multicenter	6 months of on-demand treatment with rabeprazole 10 mg	Placebo	at beginning of acute phase n=535 Mean age (SE) 47 (0.62) % male 40 Race/ethnicity NR	Adults with a history of reflux symptoms, a negative endoscopy, and 3 or more days of moderate to very severe heartburn in the 7 days entered acute phase and those that completely resolved entered RCT

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Esophagitis Grade (Grading Criteria), or other measures of symptom severity	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup, Analyzed	Study duration	Results
Bytzer 2004 International (Europe) and multicenter	Heart burn severity Moderate 64% Severe 33% Vey severe 4% Positive Helicobacter pylori test 35% Endoscopy was required to be negative for inclusion	688 screened; 535 enrolled in acute phase;117 withdrawn: 418 randomized to double bind phase (and ITT); 72 withdrawn	4 week open label acute phase followed by RCT of 6 months	rabeprazole vs.. Placebo discontinuation due to inadequate heartburn control 6% vs.. 20% p < 0.00001 Mean change in symptom severity score from baseline 0.7 vs.1.0 p < 0.05 Sufficient heartburn control (n, %) 241 (86.4) vs. 94 (67.6) p = 0.00002 Maximum duration of symptoms (days) 6.7 vs. 7.5 p = 0.0256* Maximum symptom episode duration </= 2 days (%) 30 vs. 18 p =0.0106 Maximum symptom episode duration </= 4 days (%) 59 vs. 45 p = 0.0096 Mean weekly antacid use (n) 2.0 vs. 3.9 p = 0.0009

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Withdrawals Due to Adverse Events	Funding source
Bytzer 2004 International (Europe) and multicenter	5 overall 4 rabeprazole 1 placebo	NR but 2 of the authors work for Janssen Pharmaceutica N.V., and Johnson & Johnson Pharmaceutical Services LLC

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Intervention treatment strategy (drug, dose, duration)	Comparison treatment strategy (drug, dose, duration)	Baseline demographics (age, sex, race/ethnicity)	Eligibility criteria
Caos 2000 United States Multicenter	Rabeprazole 10 or 20 mg per day for 52 weeks	Placebo	Mean age (SD) 57.0 (13.8) % male 60.3 Race/ethnicity NR	all patients had previously had erosive GERD and had been healed prior to study entry

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Esophagitis Grade (Grading Criteria), or other measures of symptom severity	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup, Analyzed	Study duration	Results
Caos 2000 United States Multicenter	baseline endoscopy modified Hetzel-Dent grade 0/1/2 151/52/0 baseline GERD heartburn frequency grade none/few/several/many/continual 116/36/18/7/25	Screened NR, Eligible NR, Enrolled 209, Randomized 209 (ITT), 101 withdrawals	52 weeks	Rabeprazole 20 mg. vs. rabeprazole 10 mg. vs.. Placebo Healing Maintainence rates 90% vs. 73% vs. 29% Heartburn relapse rates 8% vs. 16% vs. 62%

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Withdrawals Due to Adverse Events	Funding source
Caos 2000 United States Multicenter	NR	Eisai Inc., Teaneck, NJ, USA,

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Intervention treatment strategy (drug, dose, duration)	Comparison treatment strategy (drug, dose, duration)	Baseline demographics (age, sex, race/ethnicity)	Eligibility criteria
Caos 2005 United States Multicenter	Once-daily doses of 10- or 20-mg rabeprazole	Placebo	Mean age 54 % male 64 Caucasian 90.1% African-American 6.2% Asian 0.8% Other 2.8%	Participants were previously diagnosed w/ erosive/ulcerative GERD and had been healed in an acute efficacy trial;

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Esophagitis Grade (Grading Criteria), or other measures of symptom severity	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup, Analyzed	Study duration	Results
Caos 2005 United States Multicenter	NR	Screened NR, Eligible NR, Enrolled 497, Randomized 497, in first year 236 (47%) withdrew (R10 37%, R20 25.2% placebo 79.3%), over 5 years 344 (69%) withdrew (R10 62%, R20 57% placebo 88%)	1st year were 2 identical stidies collapsed into one extension study, after successful completion of 1st year (no relapse) patients could continue for up to 4 more years for a total of 5 years	At week 260 Rabeprazole 20 mg. vs. rabeprazole 10 mg. vs.. Placebo *Relapse rates* 11% vs.. 23% vs.. 63% p < 0.001 for active treatment vs. placebo *Heartburn frequency relapse rate* 39% vs.. 48% vs. 78% p < 0.001 for active treatment vs. placebo Antacid use, mean daily dose 0.17 vs. 0.24 vs. 0.24 Rates of patient well-being 86% vs. 81% vs. 67%

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Withdrawals Due to Adverse Events	Funding source
Caos 2005 United States Multicenter	45 withdrawals due to adverse events	Eisai Inc., Teaneck, NJ, USA, and by Janssen Pharmaceutica Inc., Titusville, NJ, USA.

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Intervention treatment strategy (drug, dose, duration)	Comparison treatment strategy (drug, dose, duration)	Baseline demographics (age, sex, race/ethnicity)	Eligibility criteria
Hansen 2006 281 Norweigian general practitioner clinics	Esomeprazole 20 mg daily or on demand for 6 months following 4 week	Ranitidine 150 mg bid for 6 months	Mean age 51 % male 56 Race/ethnicity NR	Patients (18 yrs or more, with symptoms of GERD 3 or more days in previous week) were enrolled in 4 week acute phase and those that had relieved symptoms were enrolled in RCT

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Esophagitis Grade (Grading Criteria), or other measures of symptom severity	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup, Analyzed	Study duration	Results
Hansen 2006 281 Norweigian general practitioner clinics	Severity of heartburn Mild 11.6% Moderate 71.1% Severe 17.4%	Screened NR, Eligible NR, Enrolled 2156, Randomized 1902 (ITT)	4 week symptom control phase followed by 6 month RCT	*Symptom improvement via Overall Treatment Evaluation questionnaire* continuous: 80.2%, on-demand: 77.8%, vs. ranitidine 47.0%; p < 0.001 for both esomeprazole groups vs. ranitadine *% of patients who were completely/very satisfied* continuous: 82.2% on-demand: 75.4%, vs. ranitidine 33.5%

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Withdrawals Due to Adverse Events	Funding source
Hansen 2006 281 Norweigian general practitioner clinics	NR	NR but several authors emplyed by AstraZeneca

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Intervention treatment strategy (drug, dose, duration)	Comparison treatment strategy (drug, dose, duration)	Baseline demographics (age, sex, race/ethnicity)	Eligibility criteria
Inadomi 2003 United States Multicenter- VA system	All patients were stepped down to single dose of lansoprazole 30 mg daily or omeprazole 20 mg daily	NA	Mean age 64.8 % male 95.7 Race/ethnicity NR Current smokers 26.5% Current Drinkers 29.9%	patients receiving greater than single-dose PPI, defined as greater than lansoprazole 30 mg daily or omeprazole 20 mg daily, for the treatment of heartburn or acid regurgitation

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Esophagitis Grade (Grading Criteria), or other measures of symptom severity	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup, Analyzed	Study duration	Results
Inadomi 2003 United States Multicenter- VA system	NR	Screened 298, Eligible 126, Enrolled 117, withdrawals 0	6 months	93 (79.5%) remained successfully stepped-down

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Withdrawals Due to Adverse Events	Funding source
Inadomi 2003 United States Multicenter- VA system	NR	U.S. Department of Veterans Affairs, Veterans Health Administration, Health Services Research and Development Service IIR 99-238-2, and in part by a grant from TAP Pharmaceuticals

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Intervention treatment strategy (drug, dose, duration)	Comparison treatment strategy (drug, dose, duration)	Baseline demographics (age, sex, race/ethnicity)	Eligibility criteria
Kovacs 1999	Lansoprazole 15 or 30 mg/day	Placebo	Mean age 52.7 % male 87.5 Race/ethnicity NR	Male or female patients, at least 18 years of age, had a history of recently healed duodenal ulcer confirmed by endoscopy within 7 days prior to initiating study treatment.

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Esophagitis Grade (Grading Criteria), or other measures of symptom severity	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup, Analyzed	Study duration	Results
Kovacs 1999	NR	Screened NR, Eligible NR, Enrolled 59, (56 ITT) withdrawals NR	12 months but all placebo patients had remitted of withdrawn by month 6	At Month 12, significantly (P < 0.001) more lansoprazole 15 mg patients (70%) and lansoprazole 30 mg patients (85%) remained healed. 82% of lansoprazole 15 mg and 76% of lansoprazole 30 mg patients remained asymptomatic during the entire study period. All placebo patients became symptomatic, experienced ulcer recurrence, or withdrew from the study by month six. Median antacid use per day Placebo 0.21 lansoprazole 15, 0.00 lansoprazole 30 0.01

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Withdrawals Due to Adverse Events	Funding source
Kovacs 1999	six patients (two placebo, three lansoprazole 15 mg and one lansoprazole 30 mg) withdrew from the study prematurely at least in part due to an adverse event	TAP Pharmaceuticals,

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Intervention treatment strategy (drug, dose, duration)	Comparison treatment strategy (drug, dose, duration)	Baseline demographics (age, sex, race/ethnicity)	Eligibility criteria
Norman Hansen 2005 281 Norwegian General Practitioner (GP) clinics	Esomeprazole 20 mg od continuously or on-demand continuously for 6 months.	ranitidine 150 mg twice-daily continuously for 6 months.	Mean age 51 % male 57 Race/ethnicity NR	Male and female patients over 18 years of age with symptoms suggestive of GERD (heartburn as the predominant symptom with or without acid regurgitation) for 3 days or more in the past 7 days

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Esophagitis Grade (Grading Criteria), or other measures of symptom severity	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup, Analyzed	Study duration	Results
Norman Hansen 2005 281 Norwegian General Practitioner (GP) clinics	11.4% mild heartburn, 70.7% moderate heartburn 17.9% severe heartburn.	Screened NR, Eligible NR, Enrolled 2156 in acute phase and 1902 (1902 ITT) in maintaimence phase, withdrawals 254 (12%)	4-week symptom control phase followed by a 6-month follow-up phase.	Esomeprazole continuous vs.. on-demand vs..Ranitidine Percentage of patients with no heartburn at 6 months 72.2 vs.. 45.1 vs.. 32.5 All three pairwise comparisons. p < 0.0001 Percentage of patients who were completely/very satisfied with study medication 82.2 vs. 75.4 vs. 33.5, continous vs. on demand p < 0.01, either esomeprazole vs. ranitidine p < 0.0001 percentage of patients who experienced at least one relapse 7 vs. 10.9 vs. 34.4, either esomeprazole vs. ranitidine p < 0.0001

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Withdrawals Due to Adverse Events	Funding source
Norman Hansen 2005 281 Norwegian General Practitioner (GP) clinics	125 (6.5%) withdrew due to adverse events	NR but 2 authors work for AstraZeneca

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Intervention treatment strategy (drug, dose, duration)	Comparison treatment strategy (drug, dose, duration)	Baseline demographics (age, sex, race/ethnicity)	Eligibility criteria
Baldi 2006	Lansoprazole 30mg in AM and Lansoprazole 30mg in PM	Lansoprazole 30mg in AM and placebo in PM	Mean age: 54.5 years (range: 29-70 years) 15.5% male Ethnicity: NR	Patients aged 18-70 years with unexplained chronic persistent cough (for ≥ 3days/week for ≥ 3 months).

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Esophagitis Grade (Grading Criteria), or other measures of symptom severity	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup, Analyzed	Study duration	Results
Baldi 2006	Severity of cough: visual analog scale (VAS) graded from 0 to 10 and to a four-level scoring system, regarding the previous week: - Overall frquency: 0=absent, 1=occasional (<3 days/week), 2=often (3-6 days/week), 3=every day - Daily frequency: 0=absent, 1=1episode, 2=2-3 episodes, 3=>3 episodes - Severity: 0=absent, 1=mild (not interfering with daily activities), 2=moderate (somtimes interfering with daily activities), 3=severe (regularly interfering with daily activities and/or sleep)	45/36/36/1/0/35	4 months	Both groups improved, with no difference between the two treatment groups. At the end of the study 10/17 and 11/18 had no cough in the 30mg/d group vs 60mg/d group, respectively.

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Withdrawals Due to Adverse Events	Funding source
Baldi 2006	None	NR

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Intervention treatment strategy (drug, dose, duration)	Comparison treatment strategy (drug, dose, duration)	Baseline demographics (age, sex, race/ethnicity)	Eligibility criteria
Bigard 2005	Lansoprazole 15mg on-demand	Placebo	Mean age: 53.3 years 45.3% male Ethnicity: NR	Male and female out-patients, aged 18-80 years, who presented with ≥3 episodes of moderate-to-severe hearburn and were asymptomatic after the acute phase.

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Esophagitis Grade (Grading Criteria), or other measures of symptom severity	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup, Analyzed	Study duration	Results
Bigard 2005	Primary efficacy point: % of patients included in this phase who completed the study in each treatment group after 6 months of on-demand treatment. Secondary efficacy point: - % of patients discontiuing the on-demand phase of the study because of insufficient hearburn control - time to study discontinuation because of unwillingness to continue for any reason - time to study discontinuation because of insufficient control of heartburn - time to study discontinuation becuase of unwillingness to continue for any reason as a function of H. pylori status - time to discontinuation because of insufficient control of hearburn as a function of H. pylori status -consumption of study medication as evaluated with Medication Event Monitoring System (MEMS) - severity of heartburn - overall assessment of study treatment efficacy - quality of life - safety	203/181/181/54/0/181	6 months	Lansoprazole vs Placebo Completion of study (ITT population): 81% vs 60.8% (p=0.003) Completion of study (per-protocol population): 81.1% vs 61.8% (p=0.009) Study discontinuation due to insufficient control of heartburn (ITT population): 15.5% vs 27.8% (p=0.046) Study discontinuation due to insufficient control of hearburn (per-protocol population): 16.2% vs 28.9% (p=0.063) Time to study discontinuation (days) ITT population: N=84 vs 97; mean=162.4 vs 136.7 (p=0.024), median=181 vs 175 Per-protocol population: N=74 vs 76, mean=161.6 vs 134.7 (p=0.018), median=181 vs175

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Withdrawals Due to Adverse Events	Funding source
Bigard 2005	3 discontinued due to Aes (2 considered related to study drug) 58 AEs were reported by 41 patients	Takeda France

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Intervention treatment strategy (drug, dose, duration)	Comparison treatment strategy (drug, dose, duration)	Baseline demographics (age, sex, race/ethnicity)	Eligibility criteria
Björnsson 2006	Gp 1: Omeprazole 20mg oid	Gp 2: Omeprazole 20mg/day for 1 week, omeprazole 10mg/day for 1 week, omeprazole 10mg every other day for 1 week	Median age: 65 years (range: 51-70 years) 45.8% male Ethnicity: NR	Patients with > 8 weeks of regular daily use of PPIs
Cibor 2006	Gp 1: Lansoprazole 30mg on-demand	Gp 2: Lansoprazole 15mg/day Gp 3: 4-week course of lansoprazole 30mg/day	Mean age: Gp 1=49 years, Gp 2=48 years, Gp 3=48 years % males: Gp 1=50, Gp 2=45, Gp 3=55 Ethnicity: NR	Male and females aged 18-71 years with non-erosive reflux disease diagnosed based on characteristic clinical presentation and endoscopic examinations. Must have mild reflux symptoms that would not affect daily activities of the patients and persisted ≥ 3 months prior to the visit.

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Esophagitis Grade (Grading Criteria), or other measures of symptom severity	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup, Analyzed	Study duration	Results
Björnsson 2006	24-h pH recording Questionnaires concerning GI symptoms and quality of life (Gastrointestinal symptom rating scale-GSRS; Psychological general well-being-PGWB)	593/286/97/1/0/96	12 months	Comparing Gp 1 to Gp 2, no significant differences except for prevalence of hiatal hernia was higher in Gp 2 than in Gp 1 (67% vs 47%, respectively; p=0.03)
Cibor 2006	Visual-Analog Scale (VAS; 0-10 points) Satisfaction was measured with the 4-point Verbal Rating Scale (VRS; 0=completely dissatisfied, 1=rather dissatisfied, 2=rather satisfied, 3=completely satisfied)	65/60/60/0/0/60	12 months	Gp 1 vs Gp 2 vs Gp 3 Mean intesnity on VAS After 1 month: vs 0.5 vs 0.3 After 3 months: 0.85 vs 0.65 vs 1.1 (p<0.05 for Gp 2 vs Gp 3) After 6 months: 1.0 vs 0.65 vs 1.55 (p<0.05 for Gp 1 vs Gp 3 and Gp 2 vs Gp 3) After 12 months: 1.1 vs 0.5 vs 1.65 (p<0.05 for Gp 1 vs Gp 2 and Gp 2 vs Gp 3) No differences between the groups was found on the VRS

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Withdrawals Due to Adverse Events	Funding source
Björnsson 2006	NR	Federation of County Councils in Sweden Faculty of Medicine, Göteborg University
Cibor 2006	None	NR

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Intervention treatment strategy (drug, dose, duration)	Comparison treatment strategy (drug, dose, duration)	Baseline demographics (age, sex, race/ethnicity)	Eligibility criteria
Giannini 2008	Gp 1: Esomeprazole 40mg/day for 4 weeks followed by esomeprazole 20mg/day for 20 weeks	Gp 2: Treatment assignment was based on basal endoscopy: Esophagitis grade A-D were treated with esompeprazole 40mg/day for first 4 weeks, while those with esophagitis (nonerosive reflux disease, NERD) were treated with esomeprazole 20mg for first 4 weeks, both followed by esomeprazole 20mg/day for 20 weeks	Mean age: 43.6 years 56.7% males 99.5% white	Patients aged 18-70 years presenting at gastroenterology centers with $\geq$ 3 months of typical symptoms suggestive of GERD and without alarm symptoms.

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Esophagitis Grade (Grading Criteria), or other measures of symptom severity	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup, Analyzed	Study duration	Results
Giannini 2008	Basal endoscopy to determine esophagitis grade Quality of Life in Reflux and Dyspepsia (QOLRAD) questionnaire Assessment of responders or nonresponders to treatment	649/616/612/82/72/429	6 months	Gp 1 vs Gp 2 % of patients reporting hearburn as the predominant symptom Week 4: 6.8% vs 6.9% (NS) Week 24: 2.6% vs 4.3% (NS) QOLRAD Emotional dimension Week 4: 6.4 vs 6.4 Week 24: 6.6 vs 6.6 Sleep dimension Week 4: 6.4 vs 6.4 Week 24: 6.6 vs 6.5 Food/drink dimension Week 4: 6.1 vs 6.1 Week 24: 6.5 vs 6.4 Vitality dimension Week 4: 6.3 vs 6.3 Week 24: 6.6 vs 6.5 Physical/social dimension Week 4: 6.4 vs 6.5 Week 24: 6.7 vs 6.7

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Withdrawals Due to Adverse Events	Funding source
Giannini 2008	7 withdrew, but reason not specified	AstraZeneca

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Intervention treatment strategy (drug, dose, duration)	Comparison treatment strategy (drug, dose, duration)	Baseline demographics (age, sex, race/ethnicity)	Eligibility criteria
Mine 2005	Lansoprazole 15mg/day for 16 weeks (no step therapy)	Lansoprazole 30mg/day for 8 weeks followed by famotidine 20mg twice a day for another 8 weeks (step down therapy 1) Lansoprazole 30mg/day for 8 weeks followed by lansoprazole 15mg/day for 8 weeks (step down therapy 2)	Mean age: 61.3 years 46.5% male Ethnicity: NR	Patients with symptomatic GERD

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Esophagitis Grade (Grading Criteria), or other measures of symptom severity	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup, Analyzed	Study duration	Results
Mine 2005	Los Angeles classification of reflux esophagitis was used for evaluation.	NR/NR/43/NR/NR/43	16 weeks	No step vs Step down1 vs Step down 2 Heartburn at 16 weeks: 0.7% vs 50% vs 0% Regurgitation at 16 weeks: 0% vs 78.6% vs 0.63% Dysphagia at 16 weeks: 0% vs 0.7% vs 0% Change of esophageal wall after 16 weeks (total wall): 13.7% vs 8.1% vs 36.2% Change of esophageal wall after 16

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Withdrawals Due to Adverse Events	Funding source
Mine 2005	NR	NR

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Intervention treatment strategy (drug, dose, duration)	Comparison treatment strategy (drug, dose, duration)	Baseline demographics (age, sex, race/ethnicity)	Eligibility criteria
Morgan 2007	Rabeprazole 20mg/day (COT)	Rabeprazole 20mg/day for 4 weeks than 20mg on-demand (ODT)	Mean age: 48 years 48% male 96% Caucasian	Male and females aged 25-65 years, with ≥ 3 months history of GERD, with hearburn as the predominant symptom, on continuous PPI therapy ≥ 1 month with adequeate heartburn control and ≤ 3 days of hearburn with ≤ 1 episode rated as moderate and hearburn rated satisfactorily or completely controlled during the last week of the acute phase.

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Esophagitis Grade (Grading Criteria), or other measures of symptom severity	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup, Analyzed	Study duration	Results
Morgan 2007	Daily diary of symptom severity	NR/331/268/26/8/234	6 months	COT vs ODT
	Quality of life questionnaire			Heartburn free days: 90% vs 65% (p<0.0001) Patients with >2 days/week of heartburn: 84% vs 41% (p<0.0001) Mean heartburn episodes: 7 vs 26 (p<0.0001) Mean episode duration: 1.4 days vs 4.4 days (p=0.0319) Proportion of weeks with 'satisfactory' or 'complete' control of heartburn: 96% vs 84% (p<0.0001)

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Withdrawals Due to Adverse Events	Funding source
Morgan 2007	7 patients reported 9 events No significant difference between groups COT vs ODT Sinusitis: <3% vs 6.1% Upper respiratory infection: 8.8% vs 6.9% Common cold: 3.7% vs 4.6% Bronchitis: 4.4% vs 3.8% Diarrhea: 3.7% vs <3% Headache: <3% vs 3.1% Influenza: <3% vs 3.1%	Janssen-Ortho Inc

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Intervention treatment strategy (drug, dose, duration)	Comparison treatment strategy (drug, dose, duration)	Baseline demographics (age, sex, race/ethnicity)	Eligibility criteria
Scholten 2005	Pantoprazole 20mg/day on-demand	Pantoprazole 40mg/day on-demand Placebo	Mean age: 52.4 years 51.1% male	Males and females aged >18 years with endoscopy confirmed non-erosive or mild GERD with frequent episodes of GERD symptoms with hearburn at ≥ moderate intesnsity for 3 consecutive days prior to inclusion and relieved from hearburn during last 3 days of acute phase.

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Esophagitis Grade (Grading Criteria), or other measures of symptom severity	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup, Analyzed	Study duration	Results
Scholten 2005	Patient diary	634/548/548/NR/NR/543	24 weeks	P20 vs P40 vs Pla Perceived average symptom load: 2.91 vs 2.71 vs 3.93 (p<0.0001 for P20 vs Pla and P40 vs Pla) Unwilling to continue for any reason: 6.50 vs 3.72 vs 18.92 % with insufficient heartburn control: 2.82 vs 0.94 vs 10.93 % with unsatisfactory treatment: 3.27 vs 1.87 vs 12.93

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Withdrawals Due to Adverse Events	Funding source
Scholten 2005	36% reported AEs Only 5% were deemed related to drug	ALTANA Pharma AG, Konstanz, Germany

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Intervention treatment strategy (drug, dose, duration)	Comparison treatment strategy (drug, dose, duration)	Baseline demographics (age, sex, race/ethnicity)	Eligibility criteria
Sjöstedt 2005	Esomeprazole 20mg/day	Esomeprazole 20mg/day on-demand	Mean age: 55 years (range: 20-87 years) 61% male Ethnicity: NR	Patients ≥ 18 years, with erosive reflux oesophagitis of LA grades A-D, history of hearburn episodes over ≥ 6 months and ≥ 4 days with hearburn episodes during the week prior to visit 1.

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Esophagitis Grade (Grading Criteria), or other measures of symptom severity	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup, Analyzed	Study duration	Results
Sjöstedt 2005	Endoscopic remission	NR/539/477/107/NR/370	6 months	Daily vs On-demand In remission at 6 months: 81% vs 58% Symptomatic relapses: 12 (5%) vs 13 (5.7%) (p=0.77) Proportion with mild hearburn during last 7 days of trial: 89% vs 66%

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Withdrawals Due to Adverse Events	Funding source
Sjöstedt 2005	Daily vs On-demand Nasopharyngitis: 1.2% vs 1.3% Abdominal pain: 1.2% vs 1.7% Gastroenteritis: 2% vs 0.4% Headache: 0.8% vs 1.3% Pneumonia: 1.2% vs 0.9% Vertigo: 0.8% vs 1.3% Diarrhea: 2.9% vs 0.4%	NR, but acknowledgements include AstraZeneca employee

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Intervention treatment strategy (drug, dose, duration)	Comparison treatment strategy (drug, dose, duration)	Baseline demographics (age, sex, race/ethnicity)	Eligibility criteria
Annibale 1998	Omeprazole 20mg/day	Ranitidine 150mg/day	Mean age: 49 years 64% males Ethnicity: NR	Patients aged 18-75 years with eroseive or ulcerative esophagitis, grade 2 or 3.

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Esophagitis Grade (Grading Criteria), or other measures of symptom severity	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup, Analyzed	Study duration	Results
Annibale 1998	Macrosopic appearance of the esophageal mucosa was scored from 0 to 4 according to the following scale: 0=normal esophageal mucosa; 1=erythema or diffusely red mucosa, edema causing accentuate folds, and no macroscopic erosions visible; 2=isolated round or linear erosions not involving the entire circumference; 3=confluent erosions involving the entire circumference; and 4=erosions as described above plus deep esophageal ulceration.	231/223/217/18/13/217	6 months	O20 vs R150 Overall symptom remision at 6 months Abstent: 54.7% vs 37.8% (p=0.019) Mild: 33% vs 36% Moderate: 9.4% vs 19.8% (p<0.05) Severe: 1% vs 4% Endoscopit Esophagitis grade at 6 months Grade 0: 86.3% vs 71.8% (p=0.03) Grade 1: 2% vs 3% Grade 2: 10.8% vs 19% Grade 3: 0% vs 4%

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Withdrawals Due to Adverse Events	Funding source
Annibale 1998	4 patients reported AEs (loss of libido, headache, itching, and leg erythema)	Schering-Plough

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Intervention treatment strategy (drug, dose, duration)	Comparison treatment strategy (drug, dose, duration)	Baseline demographics (age, sex, race/ethnicity)	Eligibility criteria
Houcke 2000	Lansoprazole 30mg every other day	Lansoprazole 15mg/day	Mean age: 55.4 years 61.5% males	Patients aged 18-75 years presenting with an oesophagitis greater than or equal to grade II and treated with a PPI for 4 to 8 weeks and had an endoscopically proved healed oesophagitis and were asymptomatic.

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Esophagitis Grade (Grading Criteria), or other measures of symptom severity	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup, Analyzed	Study duration	Results
Houcke 2000	Endoscopi relapse of oesophagitis was primary outcome, defined by an oesophagitis greater than or equal to grade II or symptomatic relapse defined as the recurrence of hearburn for at least 3 days and/or 3 nights during the same week or requiring treatment with Maalox for 3 consecutive days, and indicated than an endoscopy was to be performed.	NR/NR/52/10/5/52	6 months	L30 vs L15 Endsoscopic relapse at 6 months: 36% vs 25.9% (NS) Symptomatic relapse at 6 months: 28% vs 14.8% (NS) An aggravation of hearburn and functional handicap was noted in L30 ($p<0.05$) after 6 months, whereas symptomatology of L15 remained stable.

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Withdrawals Due to Adverse Events	Funding source
Houcke 2000	8 patients had 9 AEs (only 1 was noted to be related to study drug)	NR

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Intervention treatment strategy (drug, dose, duration)	Comparison treatment strategy (drug, dose, duration)	Baseline demographics (age, sex, race/ethnicity)	Eligibility criteria
Vakil 2001	Esomeprazole 40mg/day	Esomeprazole 20mg/day or Esomeprazole 10mg/day or Placebo	Mean age: 44.9 years (range: 18-84) 61.6% males 92.5% Caucasian 5.9% Black 1.6% Other	Males and non-pregnant, non-lactating females between 18-7ey5 ars, who had confirmed healing of erosive oesophagitis, no record of any serious adverse event related to study medicaiton in the healy study, and who were negative for H pylori

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Esophagitis Grade (Grading Criteria), or other measures of symptom severity	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup, Analyzed	Study duration	Results
Vakil 2001	Primary efficacy endpoint was LA Classification Grade of 'not present' based on esophagogastroduodenoscopy.	NR/NR/375/184/	6 months	E40 vs E20 vs E10 vs Pla Cumulative healing at 6 months: 87.9% vs 78.7% vs 54.2% 29.1% (p<0.001) Mean time to recurrence (days): 130 vs 101 vs 80 vs 46 Hearburn free at 1 month: 71.3% vs 63.7% vs 50.6% vs 15.5% (all P-values <0.001) Either none or only mild GERD symptoms at 1 month: 95.4% vs 87.9% vs 85.5% vs 33.3% (all P-values <0.001)

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Withdrawals Due to Adverse Events	Funding source
Vakil 2001	E40 vs E20 vs E10 vs Pla Patients with >1 AE: 31.5% vs 37.8% vs 34.1% vs 29.3% Events: Headache: 4.3% vs 4.1% vs 6.6% vs 4.3% Abdominal pain: 2.2% vs 3.1% vs 1.1% vs 2.2% Diarrhea: 1.1% vs 3.1% vs 4.4% 3.3% Flatulence: 3.3% vs 2.0% vs 1.1% vs 1.1% Gastritis: 3.3% vs 3.1% vs 0% vs 5.4% Nausea: 2.2% vs 1.0% vs 2.2% vs 2.2% Respiratory infection: 4.3% vs 4.1% vs 3.3% vs 0%	NR, but one author is employee of AstraZeneca

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Intervention treatment strategy (drug, dose, duration)	Comparison treatment strategy (drug, dose, duration)	Baseline demographics (age, sex, race/ethnicity)	Eligibility criteria
Talley 2002a	Esomeprazole 40mg on-demand	Esomeprazole 20mg on-demand or Placebo	Mean age: 48.2 years (range: 18-80 years) 45% males Ethnicity: NR	Patients with endoscopy-negative GORD, who had completed a short-term comparative study of esomprazole 20mg or 40mg and omeprazole 20mg, and who achieved complete resolution of heartburn during the last 7 days of the trial.

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Esophagitis Grade (Grading Criteria), or other measures of symptom severity	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup, Analyzed	Study duration	Results
Talley 2002a	Assessments included: -heartburn frequency -heartburn severity -severity of other GORD symptoms -severity of other gastrointestinal symptoms Primary efficacy endpoint was time to study discontinuation due to unwillingness to continue for any reason.	NR/NR/721/177/26/721	6 months	E40 vs E20 vs Plac <u>Unwilling to continue</u> General: 11.3% vs 7.8% vs 41.8% (both P-values <0.0001) Due to insufficient control of heartburn: 8.5% vs 5% vs 36.3% (both P-values <0.0001) Due to AE: 0.7% vs 1.4% vs 4.8% Due to other reasons: 2.1% vs 1.4% vs 0.7% Proportion of patients free form heartburn after 6 months: 35% vs 30% vs 16% Proportion of patients from from regurgitation after 6 months: 62% vs 62% vs 35% Proportion of patients from from epigastric pain after 6 months: 67% vs 61% vs 40%

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Withdrawals Due to Adverse Events	Funding source
Talley 2002a	E40 vs E20 vs Pla Withdrawals due to AEs: 2.3% vs 3.5% vs 2% Reporting of AEs: 73.7% vs 67% vs 66.4% Most commonly reported AEs in E40 and E20 groups: respiratory infection (11-12%), diarrhoea (8%), headache (8%), and back pain (3-9%)	NR

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Intervention treatment strategy (drug, dose, duration)	Comparison treatment strategy (drug, dose, duration)	Baseline demographics (age, sex, race/ethnicity)	Eligibility criteria
Talley 2002b	Pantoprazole 20mg/day	Ranitidine 150mg twice a day	Mean age: 52.5 years 47.6% males 96.4% white	Adults ≥ 18 years who presented with symptomatic GORD and reported experiencing heartburn ≥ 2/week as the predominant upper-gastrointestinal complaint.

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Esophagitis Grade (Grading Criteria), or other measures of symptom severity	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup, Analyzed	Study duration	Results
Talley 2002b	Primary endpoint was: symptom control rate Complete symptom control is defined as the absence of any episodes of heartburn during the seven days before follow-up. Sufficient symptom control is defined as a mild episode of heartburn experienced on not more than one day during the seven days before follow-up. GSRS questionnaire used as well.	NR/NR/307/123/4/307	12 months	P vs R <u>Complete symptom control</u> At 6 months: 71% vs 56% (p=0.007) At 12 months: 77% vs 59% (p=0.001) <u>Sufficient symptom control</u> At 4 weeks: 64% vs 48% (p=0.008) At 12 months: 86% vs 79% (NS)

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Withdrawals Due to Adverse Events	Funding source
Talley 2002b	P vs R Withdrawals due to AEs: 12% vs 14%	Pharmacia Australia Pty Limited

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Intervention treatment strategy (drug, dose, duration)	Comparison treatment strategy (drug, dose, duration)	Baseline demographics (age, sex, race/ethnicity)	Eligibility criteria
Venables 1997	Omeprazole 10mg/day	Placebo	Mean age: 50.5 years 45.8% males Ethnicity: NR	Patients aged ≥ 18 years with hearburn as the predominant symptom of GORD for ≥ 3 months, who had non-erosive oesophagitis at endoscopy and had obtained successful control of heartburn after 4 or 8 weeks' initial therapy.

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Esophagitis Grade (Grading Criteria), or other measures of symptom severity	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup, Analyzed	Study duration	Results
Venables 1997	Severity of heartburn during last 7 days before each visit. Graded as none, mild (awareness of sign or symptom but easily tolerated), moderate (discomfort sufficient to cause interference with normal activities), or sever (iincapacitating, with inability to perform normal activities) Frequency of heartburn was recorded as the number of days with episodes during the last 7: none, 1 day, 2-4 days, 5-6 days, or 7 days Other symptoms were also graded in severity (regurgitation, dysphagia, epigastric pain, and nausea)	NR/495/495/	6 months	O10 vs Pla Life-table estimates for cumulative relapse rates (unwillingness to continue in study) at 6 months: 27% vs 52% (p=0.0001) # of relapses At 1 month: 9 vs 49 (p=0.0001) At 6 months: 45 vs 119 (p=0.0001) % experiencing heartburn At 8 weeks: 47% vs 60% (p<0.01) At 16 weeks: 37% vs 56% (p<0.001) % experiencing regurgitation At 8 weeks: 22% vs 38% (p<0.001) % experiencing epigastric pain At 16 weeks: 13% vs 27% (p<0.01) All other symptoms experiences were NS

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Withdrawals Due to Adverse Events	Funding source
Venables 1997	O10 vs Pla Withdrawals due to AEs: 5.7% vs 10.6%	Astra Pharmaceuticals Ltd monitored the study

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Intervention treatment strategy (drug, dose, duration)	Comparison treatment strategy (drug, dose, duration)	Baseline demographics (age, sex, race/ethnicity)	Eligibility criteria
Bate 1995	10 mg omeprazole once daily (n=61), 20 mg omeprazole once daily (n=69), for one year or until symptomatic relapse.	placebo (n=63) for one year or until symptomatic relapse.	Mean age 53 % male 74 Race/ethnicity NR	age 18-80 years, minimum of three months' history of symptoms of gastro-oesophageal reflux disease,and grade 2-4 reflux oesophagitis on endoscopy and each patient had to have been rendered healed (grade 0 on endoscopy) and symptom free (grade 0 on patient's overall assessment) after their initial treatment with omeprazole.

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Esophagitis Grade (Grading Criteria), or other measures of symptom severity	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup, Analyzed	Study duration	Results
Bate 1995	Patients (%) with each grade of oesophagitis Grade 0 0% Grade 1 0 % Grade 2 68% Grade 3 27% Grade 4 5% Grade 1 - no macroscopic erosions visible; erythema or diffusely red mucosa; oedema causing accentuated folds. Grade 2 - isolated round or linear erosions extending from the squamocolumnar junction upwards in relation to the folds, but not involving the entire circumference. Grade 3 - confluent erosions involving the entire circumference. Grade 4 - frank benign ulcer.	193 of 200 patients both healed of reflux oesophagitis and rendered asymptomatic from 313 patients 3 LTF	up to one year	Omeprazole 10 vs. Omeprazole 20 vs Placebo Remission at 12 months 77% (95% CI 64 to 89%) vs. 83% (95% CI 73 to 93%) vs. 34% (16 to 52%) each omeprazole p<0001 vs placebo

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Withdrawals Due to Adverse Events	Funding source
Bate 1995	NR	NR

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Intervention treatment strategy (drug, dose, duration)	Comparison treatment strategy (drug, dose, duration)	Baseline demographics (age, sex, race/ethnicity)	Eligibility criteria
Escourrou 1999 52 centres in Belgium, France, Italy and the Netherlands.	pantoprazole 20 mg (n = 203) for one year	pantoprazole 40 mg (n=ˆ 193) for one year	Median age 50 % male 72.4 Race/ethnicity NR	18 to 88 years old) with healed reflux oesophagitis (grade II or III before healing)

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Esophagitis Grade (Grading Criteria), or other measures of symptom severity	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup, Analyzed	Study duration	Results
Escourrou 1999 52 centres in Belgium, France, Italy and the Netherlands.	grade II (82%) or III (18%), according to the Savary-Miller classi®cation.	460 acute in healing phase, 396 enrolled in long-term, 84 discontinuations	4 to 8 weeks acute treatment plus one year	Pantoprazole 20 vs.. Pantoprazole 40 Endoscopic relapse 49 (24%) vs.. 30 (16%)

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Withdrawals Due to Adverse Events	Funding source
Escourrou 1999 52 centres in Belgium, France, Italy and the Netherlands.	3 withdrawals due to adverse events	Nycomed Pharma, Roskilde, Denmark and Byk Gulden Pharmaceuticals, Konstanz, ermany.

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Intervention treatment strategy (drug, dose, duration)	Comparison treatment strategy (drug, dose, duration)	Baseline demographics (age, sex, race/ethnicity)	Eligibility criteria
Festen 1999	Omeprazole 20 mg per day for one year	Ranitidine 600 mg per day for one year	Mean age 50 % male 52.2 Race/ethnicity NR	18–80 yr with esophagitis grade I or II (Savary-Miller)

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Esophagitis Grade (Grading Criteria), or other measures of symptom severity	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup, Analyzed	Study duration	Results
Festen 1999	Grade of esophagitis, 0/1/2 <1%, 73.3%, 26.7% (Savary-Miller)	Screened NR 448 enrolled in acute phase and 264 in maintainence phase and 263 randomized,	4 to 8 weeks acute treatment plus one year	number of patients in remission within 12 months of maintenance treatment were omeprazole 68% and ranitidine 39% rates of remission by acute and maintainence treatments ranitidine /omeprazole 74%; omeprazole/omeprazole 65%; ranitidine /ranitidine 45%; and omeprazole /ranitidine 35%, respectively (p < 0.0001)

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Withdrawals Due to Adverse Events	Funding source
Festen 1999	17 withdrawals due to adverse events	Astra Pharmaceutica BV

Evidence Table 14. Long term harms in observational studies

Author, year Country	Study design	Study objective	Time period covered	Data source	Sample size	Population characteristics
Davies, 2008 UK	Cohort, retrospective	To monitor the safety of esomeprazole prescribed to patients by primary care physicans/general practitioners in England.	September 2000 through April 2001	Prescription Pricing Authority	13,263	Median age (years): Male: 54, Female: 58 46.1% males
Dial, 2005 UK	Population-based case-control	To evaluate whether the use of gastric acid–suppressant drugs is associated with the risk of communityacquired CDAD.	January 1, 1994 through December 31, 2004	United Kingdom General Practice Research Database	1,672 cases 16,720 controls	Ages of Cases (years) ≤ 35: 5% 36-50: 7% 51-65: 12% >65: 76% Age of Controls (years) ≤ 35: 26% 36-50: 28% 51-65: 24% >65: 22% 46.8% males

Evidence Table 14. Long term harms in observational studies

Author, year Country	Statistical methods	Effectiveness outcomes
Davies, 2008 UK	Incidence densities were calculated for all reported events during treatment within specified time periods and expressed as the number of first reports of an event per 1000 patient-months of exposure.	15.7% stopped taking esomeprazole due to 'condition improved'
Dial, 2005 UK	Conditional logistic regression was used to estimate the odds ratio as an approximation of the rate ratio (RR) of CDAD for the risk factors under study.	1233 cases (400 were identified based on a clinical diagnosis and 833 were identified based on a positive toxin assay) were not hospitalized during the prior year and were matched with controls. Cases had a mean age of 71 years and were more likely to be women compared to their age-matched controls. Cases were also more likely to have a history of renal failure, inflammatory bowel disease, malignancy, and to be methicillin-resistant *Staphylococcus aureus* -positive.

Evidence Table 14. Long term harms in observational studies

Author, year Country	Safety Outcomes	Comments	Funder
Davies, 2008 UK	<u>AE given as reason for stopping treatment (N)</u> Diarrhoea (66) Dyspepsia (61) Intolerance (60) Nausea/vomiting (55) Headache/migraine (43) Pain abdomen (33) Rash (25) Unspecified side effects (25) Malaise/lassitude (25) Pruritus (21)		Funds were received from Nexium, but the did not sponsor the study.
Dial, 2005 UK	<u>Adjusted RR</u> Current PPI exposure: 2.9 (95% CI, 2.4-3.4) H_2RA: 2.0 (95% CI, 1.6-2.7) Current exposure to NSAIDs, but not aspirin was associated with an increased rate of *C difficile* (RR, 1.3; 95% CI, 1.2-1.5) <u>Associated with an increase risk of community-acquired CDAD</u> Renal failure: adjusted RR, 3.7; 95% CI, 2.4-5.6 Inflammatory bowel disease: RR, 3.6; 95% CI, 2.6-5.1 Malignancy: RR, 1.9; 95% CI, 1.4-2.7 Being methicillin-resistant *Staphylococcus aureus*- positive: RR, 4.2; 95% CI, 2.7-6.4		Canadian Institutes of Health Research and the Canadian Foundation for Innovation

Evidence Table 14. Long term harms in observational studies

Author, year Country	Study design	Study objective	Time period covered	Data source	Sample size	Population characteristics
Yang, 2007 UK	Nested case-control	To determine whether long-term PPI therapy is associated with an increased risk of CRC in a large population-representative cohort with up to 15 years (1987–2002) of follow-up from the United Kingdom.	May 1987 through April 2002	General Practice Research Database	4432 cases 44292 controls	Mean age at database enrollment (years): Cases: 67.5 vs Controls: 63.6 (p<0.0001) % males: Cases: 54.5 vs Controls: 44.2 (p<0.001) % nonsmoker: Cases: 22.7 vs Controls 22.0 (p=0.04) % alcohol users: Cases: 38.6 vs Controls 36.8 (p=0.01) % HRT use: Cases: 1.3 vs Controls: 3.7 (p<0.001) % NSAID/aspirin use: Cases: 7.8% vs Controls: 10% (p<0.001) % H2RA use: Cases: 5.5 vs Controls: 4.2 (p<0.001) % with colonoscopy or flexible sigmoidoscopy 1 year before index date: Cases: 5.5 vs Controls: 2.4 (p<0.001) % pernicious anemia: Cases: 0.7 vs Controls: 0.56 (p=0.24)

Evidence Table 14. Long term harms in observational studies

Author, year Country	Statistical methods	Effectiveness outcomes
Yang, 2007 UK	Conditional logistic regression was used to estimate the odds ratios (ORs) and 95% CI	NR

Evidence Table 14. Long term harms in observational studies

Author, year Country	Safety Outcomes	Comments	Funder
Yang, 2007 UK	ORs for Colorectal Cancer Associated with PPI therapy (nonusers are used as reference) **<1 year use, within 12months of index date** Cases: 9% vs Controls: 3.8% (adjusted OR, 2.6; 95% CI, 2.3-2.9; p<0.001) **<1 year use, more than 12months before index date** Cases: 4.8% vs Controls: 4.6% (adjusted OR, 1.1; 95% CI, 0.9-1.3; p=0.3) **1-2 years of use** Cases: 1.51% vs Controls: 1.3% (adjusted OR, 1.2; 95% CI, 0.9-1.6; p=0.2) **2-3 years of use** Cases: 0.8% vs Controls: 0.9% (adjusted OR, 0.9; 95% CI, 0.6-1.3; p=0.6) **3-4 years of use** Cases: 0.5% vs Controls: 0.5% (adjusted OR, 1.1; 95% CI, 0.7-1.7; p=0.7) **4-5 years of use** Cases: 0.4% vs Controls: 0.3% (adjusted OR, 1.1; 95% CI, 0.7-1.9; p=0.6) **>5 years of use** Cases: 0.4% vs Controls: 0.3% (adjusted OR, 1.1; 95% CI, 0.7-1.9; p=0.7)	For the country: authors are in US, but data is pulled from UK database	National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases Mentored Career Development Award

Evidence Table 14. Long term harms in observational studies

Author, year Country	Study design	Study objective	Time period covered	Data source	Sample size	Population characteristics
Yang, 2006 UK	Nested case-control	To determine whether opposing effects of PPI therapy on bone metabolism translate into clinically important alterations in hip fracture risk in a large cohort representative of the general population.	May 1987 through March 2003	General Practice Research Database	13,556 Cases 135,386 Controls	Mean age at database enrollment (years): Cases: 77 vs Controls: 77 % males: Cases: 20.1 vs Controls: 20.11 % with BMI <20: Cases: 6.77 vs Controls: 3.59 % with BMI >30: Cases: 4.51 vs Controls: 6.71 % current smokers: Cases: 13.68 vs Controls 9.65 % alcoholism: Cases: 1.93 vs Controls 0.42 % with arthritis: Cases: 29.85 vs Controls: 24.56 % with history of stroke: Cases: 13.96 vs Controls: 7.23 % with asthma or COPD: Cases: 11.67 vs Controls: 8.02 % with dementia: Cases: 11.07 vs Controls: 3.57 % with DM: Cases: 4.40 vs Controls: 2.94 % with congestive heart failure: Cases: 6.72 vs Controls: 4.52 % with impaired mobility: Cases: 6.14 vs Controls: 2.47 % with prior MI: Cases: 5.28 vs Controls: 4.33 % with peptic ulcer disease: Cases: 4.34 vs Controls: 2.87 % with seizure disorder: Cases: 3.16 vs Controls: 1.03 % with peripheral vascular disease: Cases: 5.39 vs Controls: 3.59 Visual impairment 2.16 1.53 1.43 (1.26 1.62)

Evidence Table 14. Long term harms in observational studies

Author, year Country	Statistical methods	Effectiveness outcomes
Yang, 2006 UK	Conditional logistic regression was used to estimate the unadjusted and adjusted Ors and 95% CI	NR

Evidence Table 14. Long term harms in observational studies

Author, year Country	Safety Outcomes	Comments	Funder
Yang, 2006 UK	Adjusted ORs for Hip Fracture Associated with PPI therapy (nonusers are used as reference) 1 year of use: 1.22 (95% CI, 1.15-1.30) 2 years of use: 1.41 (95% CI, 1.28-1.56) 3 years of use: 1.54 (95% CI, 1.37-1.73) 4 years of use: 1.59 (95% CI, 1.39-1.80) >1 year of use with average daily dose ≤1.75: 1.40 (95% CI, 1.26-1.54) >1 year of use with average daily dose >1.75: 2.65 (95% CI, 1.80-3.90) Adjusted ORs for Hip Fracture Associated with H2RA therapy (nonusers are used as reference) >1 year of use with average daily dose ≤ 1.75: 1.23 (95% CI, 1.09-1.40) >1 year of use with average daily dose >1.75: 1.30 (95% CI, 1.16-1.46)	For the country: authors are in US, but data is pulled from UK database	The American Gastroenterological Association and GSK Institute for Digestive Health Award

Evidence Table 14. Long term harms in observational studies

Author, year Country	Study design	Study objective	Time period covered	Data source	Sample size	Population characteristics
Estborn, 2006 Sweden	Retrospective cohort	To investigate the occurrence of community-acquired respiratory tract infection, including pneumonia, n patients receiving esomeprazole vs placebo and other acid-suppressive agents in RCTs.	NR	AstraZeneca ARIADNE safety database	28,627	Median age (years): esomeprazole: 48 vs Placebo and other drugs: 47 57.7% males 98.6% white

Evidence Table 14. Long term harms in observational studies

Author, year Country	Statistical methods	Effectiveness outcomes
Estborn, 2006 Sweden	RR values, adjusted for treatment duration, were calculated for each group of events	NR

Evidence Table 14. Long term harms in observational studies

Author, year Country	Safety Outcomes	Comments	Funder
Estborn, 2006 Sweden	Esomeprazole vs Placebo RRs for all respiratory tract infections were 0.93 (99% CI, 0.78-1.11) RRs for signs and symptoms potentially indicating a respiratory tract infection was 0.85 (99% CI, 0.57-1.27) RRs for lower respiratory tract infection was 0.92 (99% CI, 0.59-1.42) RRs for pneumonia was 0.94 (99% CI, 0.29-3.07)		AstraZeneca

Evidence Table 14. Long term harms in observational studies

Author, year Country	Study design	Study objective	Time period covered	Data source	Sample size	Population characteristics
Kaye, 2008 UK	Nested case-control	To estimate the relative risk of hip fracture associated with PPI use in a population without major risk factors.	1995 and 2005	United Kingdom General Practice Research Database	1098 cases 10,923 controls	Cases vs Controls Age 50-59 years: 13.4% vs 13.4% Age 60-69 years: 26.0% vs 26.0% Age 70-79 years: 60.7% vs 60.5% 28.4% males Nonsmokers: 45.8% vs 53.6% BMI <24: 31.2% vs 24.0% BMI 24-28: 25.4% vs 30.3% BMI>28: 15.0% vs 22.4 Unknown BMI: 28.3% vs 23.3%

Evidence Table 14. Long term harms in observational studies

Author, year Country	Statistical methods	Effectiveness outcomes
Kaye, 2008 UK	Conditional logistic regression to estimate odds ratios and 95% Cis for various categoric levels of exposure to any PPI or each PPI individually.	NR

Evidence Table 14. Long term harms in observational studies

Author, year Country	Safety Outcomes	Comments	Funder
Kaye, 2008 UK	RR for hip fracture (cases vs controls) 1 PPI prescription: 3.8% vs 3.7%; RR, 1.0 (95% CI, 0.7-1.4) 2-9 PPI prescriptions: 4.8% vs 4.8%; RR, 1.0 (95% CI, 0.7-1.3) 10-29 PPI prescriptions: 2.4% vs 2.6%; RR, 0.9 (95% CI, 0.6-1.4) ≥ 30 PPI prescriptions: 1.0% vs 2.0%; RR, 0.5 (95% CI, 0.3-0.9) 1 Omeprazole prescription: 2.3% vs 2.8%; RR, 0.8 (95% CI, 0.5-1.2) 2-9 Omeprazole prescriptions: 2.9% vs 3.0%; RR, 0.9 (95% CI, 0.7-1.4) 10-29 Omeprazole prescriptions: 1.5% vs 1.7%; RR, 0.9 (95% CI, 0.5-1.4) ≥ 30 Omeprazole prescriptions: 0.2% vs 1.2%; RR, 0.2 (95% CI, 0.040.6) 1 Lansoprazole prescription: 2.0% vs 2.0%; RR, 1.0 (95% CI, 0.6-1.6) 2-9 Lansoprazole prescriptions: 2.4% vs 2.3%; RR, 1.0 (95% CI, 0.7-1.5) 10-29 Lansoprazole prescriptions: 0.9% vs 1.0%; RR, 0.9 (95% CI, 0.5-1.7) ≥ 30 Lansoprazole prescriptions: 0.6% vs 0.5%; RR, 1.3 (95% CI, 0.6-2.8) 1 Pantoprazole prescription: 0.6% vs 0.2%; RR, 2.7 (95% CI, 1.1-6.7) 2-9 Pantoprazole prescriptions: 0.2% vs 0.3%; RR, 0.6 (95% CI, 0.1-2.3) 10-29 Pantoprazole prescriptions: no estimate could be obtained ≥ 30 Pantoprazole prescriptions: 0.1% vs 0.1%; RR, 1.0 (95% CI, 0.1- 1 Rabeprazole prescription: 0.2% vs 0.4%; RR, 0.5 (95% CI, 0.1-1.9) 2-9 Rabeprazole prescriptions: 0.6% vs 0.4%; RR, 1.8 (95% CI, 0.8-4. 10-29 Rabeprazole prescriptions: 0.1% vs 0.2%; RR, 0.5 (95% CI, 0.1 ≥ 30 Rabeprazole prescriptions: 0.1% vs 0.1%; RR, 1.6 (95% CI, 0.2-1		NR

Evidence Table 14. Long term harms in observational studies

Author, year Country	Study design	Study objective	Time period covered	Data source	Sample size	Population characteristics
Laheij, 2004 Netherlands	Population-based cohort	To examine the association between the use of gastric acid-suppressive drugs and community-acquired pneumonia	January 1, 1995 through December 31, 2002	Integrated Primary Care Information Project, a gneral research database	475 cases 4960 controls	Age (years) <20: 0.07% 20-40: 11% 41-60: 30.8% >60: 58.13% 44.3% males 9.7% with DM 10% with heart failure 21% with chronic obstructive lung disease 0.4% with stomach cancer 0.82% with lung cancer 3.1% with current use of immunosuppressants 70.2% with no use of antibiotics in last year 17.9% with 1 antibiotic use in last year 11.9% with $\geq$ 2 antibiotics used in last year

Evidence Table 14. Long term harms in observational studies

Author, year Country	Statistical methods	Effectiveness outcomes
Laheij, 2004 Netherlands	Conditional logistic regression analysis adjusted for all covariates that were univariately associated with pneumonia (p<.10)	NR

Evidence Table 14. Long term harms in observational studies

Author, year Country	Safety Outcomes	Comments	Funder
Laheij, 2004 Netherlands	Adjusted ORs for community-acquired pneumonia in patients using PPIs or H_2RAs Current use of acid-suppressive drugs: 1.27 (95% CI, 1.06-1.54) Recent (<30 days ago) use of acid-suppressive drugs: 1.08 (95% CI, 0.78-1.50) Past (30-180 days ago) use of acid-suppressive drugs: 1.00 (95% CI, 0.74-1.36) Current use of PPIs: 1.73 (95% CI, 1.33-2.25) Current use of H_2RAs: 1.59 (95% CI, 1.14-2.23) Current use of PPIs and H_2RAs: 1.76 (95% CI, 1.18-2.61) Recent use of PPIs or H_2RAs: 1.44 (95% CI, 0.94-2.21) Omeprazole alone: 1.74 (95% CI, 1.28-2.35) Pantoprazole alone: 2.29 (95% CI, 1.43-3.68) Lansoprazole alone: 0.91 (95% CI, 0.35-2.34) Cimetidine alone: 0.62 (95% CI, 0.18-2.11) Ranitidine alone: 1.82 (95% CI, 1.26-2.64) Famotidine alone: 1.58 (95% CI, 0.64-3.93)		NR

Evidence Table 14. Long term harms in observational studies

Author, year Country	Study design	Study objective	Time period covered	Data source	Sample size	Population characteristics
Lowe, 2006 Canada	Population-based, nested case-control	Determine whether outpatient PPI use influences the risk of hospital admission for CDAD among older patients who have recently been treated with antibiotics.	April 1, 2002 through March 31, 2005	Ontario Drug Benefit Program database	1,389 cases 12,303 controls	Mean age (years): 78.4 60.4% males Penicillin use within 60 days: 20.3% Cephalosporin use within 60 days: 24.7% Macrolides use within 60 days: 20.5% Fluroquinolones use within 60 days: 36.4% Trimethoprim-sulfamethaxazole use within 60 days: 6.7% Clindamycin use within 60 days: 8.6% Tetracyclines use within 60 days: 0.7% Nitrofurantoin use within 60 days: 6.5%

Evidence Table 14. Long term harms in observational studies

Author, year Country	Statistical methods	Effectiveness outcomes
Lowe, 2006 Canada	Conditional logistic regressions were used to estimate the OR and 95% CI	NR

Evidence Table 14. Long term harms in observational studies

Author, year Country	Safety Outcomes	Comments	Funder
Lowe, 2006 Canada	Association between outpatient PPI use and hospitalization for *Clostridium difficile* -associated disease (CDAD) ≤ 90 days since PPI exposure Cases: 22.0% vs Controls: 18.3%; Adjusted OR, 0.9 (95% CI, 0.8-1.1) 91-180 days since PPI exposure Cases: 2.2% vs Controls: 2.7%; Adjusted OR, 0.7 (95% CI, 0.5-1.0) 181-365 days since PPI exposure Cases: 2.7% vs Controls: 2.6%; Adjusted OR, 0.9 (95% CI, 0.6-1.3)		New Investigator Award from the New Emerging Teams grant of the Canadian Institutes of Health Research and a New Investigator Award from the Canadian Instistutes of Health Research

Evidence Table 14. Long term harms in observational studies

Author, year Country	Study design	Study objective	Time period covered	Data source	Sample size	Population characteristics
Salgueiro, 2006 Spain	Case-series	To evaluate similarities and differences in safety among PPIs under the usual conditions of prescription.	January 1, 2004 through December 31, 2004	Spanish Pharma-covigilance System Database	680 reports of uses of PPIs	Median age: 62 years (range: 12-92) 40% male

Evidence Table 14. Long term harms in observational studies

Author, year Country	Statistical methods	Effectiveness outcomes
Salgueiro, 2006 Spain	Odds ratio (OR) was calculated by constructing a 2 X 2 contingency table for each organ and system affected and each PPI, adjusted to the interval of search.	NR

Evidence Table 14. Long term harms in observational studies

Author, year Country	Safety Outcomes	Comments	Funder
Salgueiro, 2006 Spain	ORs for Skin and appendage disorders Omeprazole: 1.4 (95% CI, 1.2-1.7) Rabeprazole: 1.9 (95% CI, 1.1-3.2) ORs for Urinary System Lansoprazole: 2.7 (95% CI, 1.2-6.2) ORs for Reproductive female Lansoprazole: 4.2 (95% CI, 1.5-11.4) ORs for Endocrine disorders Lansoprazole: 4.0 (95% CI, 1.3-12.7) ORs for Musculoskeletal system disorders Omeprazole: 1.8 (95% CI, 1.3-2.4) Esomeprazole: 2.9 (95% CI, 1.2-7.4) ORs for vision disorders Pantoprazole: 3.0 (95% CI, 1.5-6.1) Rabeprazole: 4.0 (95% CI, 1.6-10.0) Esomeprazole: 3.4 (95% CI, 1.1-11.1) ORs for gastrointestinal system disorders Omeprazole: 1.8 (95% CI, 1.5-2.1) Lansoprazole: 2.4 (95% CI, 1.6-3.7) ORs for liver and biliary system disorders Omeprazole: 1.7 (95% CI, 1.2-2.4) Lansoprazole: 2.4 (95% CI, 1.1-5.1) Pantoprazole: 3.0 (95% CI, 1.7-5.5)		NR

Evidence Table 14. Long term harms in observational studies

Author, year Country	Study design	Study objective	Time period covered	Data source	Sample size	Population characteristics
Sarkar, 2008 UK	Nested case-control	To examine the association between PPI use and CAP in adults followed in a general practice.	1987 to 2002	The General Practice Research Database in the UK	80,066 Cases 799,881 Controls	Cases vs Controls Mean age (years): 73.5 vs 43.5 Males: 47.4% vs 52.6% Alcoholism: 2.3% vs 1.5% Dysphasia: 1.8% vs 0.9% Dementia: 14.4% vs 1.5% Stroke: 19.2% vs 3.5% Diabetes: 4.9% vs 2.6% Cirrhosis: 0.3% vs 0.1% Renal failure: 0.5% vs 0.1% Congestive heart failure: 10.5% vs 1.8% MI: 9.3% vs 3.3% COPD or asthma: 22.4% vs 10.3% Cancer: 7.3% vs 4.2% Previous CAP: 3.2% vs 0.9% Current smoker: 14.5% vs 15.9%
Tahir, 2007 US	Systematic review	To review the influence of PPIs on calcium absoprtion, bone remodeling, and fracture risk.	1966-April 2007	MEDLINE	NR	NR
Targownik, 2008 Canada	Retrospective matched cohort	To examine the effects of longer durations of PPI use on the development of osteoporosis-related fractures.	April 1996 through March 2004	Population Health Research Data Repository	15,792 cases 47,289 controls	Cases vs Controls Age 50-59 years: 17.4% vs 17.7% Age 60-69 years: 19.9% vs 19.8% Age 70-79 years: 28.6% vs 29.1% Age $\geq$ 80 years: 34.1% vs 33.4% Male: 29.7% vs 29.8%

Evidence Table 14. Long term harms in observational studies

Author, year Country	Statistical methods	Effectiveness outcomes
Sarkar, 2008 UK	Adjusted ORs were estimated by using conditional logistic regression, adjusting for potential confounders.	NR
Tahir, 2007 US	NR	NR
Targownik, 2008 Canada	Conditional logistic regression model to generage odds ratios (OR) and 95% confidence intervals (CI)	NR

Evidence Table 14. Long term harms in observational studies

Author, year Country	Safety Outcomes	Comments	Funder
Sarkar, 2008 UK	Adjusted OR for CAP associated with PPI use within 30 days of the index date: 2.05 (95% CI, 1.96-2.15; p<0.001) Adjusted OR for CAP associated with current histamine-2-receptor antagonist use: 0.99 (95% CI, 0.95-1.04; p=0.78) Adjusted OR for CAP associated with being a new user of a PPI within 30 days of the index date: 2.45 (95% CI, 2.04-2.95; p<0.001)		Academic Development fund by the Department of Medicine, University of Pennsylvania
Tahir, 2007 US	There is conflicting evidence about whether PPIs cause decreased calcium absorption.	This is a review article, there do not do their own meta-analysis, instead they describe all the studies, without really synthesizing the data.	NR
Targownik, 2008 Canada	≥ 7 years of PPI use has a statistically significant association between use of PPI and any osteoporosis-related fracture (adjusted OR 1.92; 95% CI, 1.16-3.18) ≥ 5 years of PPI use was associated with an increased risk of hip fracture (adjusted OR 1.62, 95% CI, 1.02-2.58) Magnitutde of risk increased with increasing duration of exposure to PPIs: ≥6 years, adjusted OR 2.49, 95% CI, 1.33-4.67; ≥ 7 years, adjusted OR 4.55, 95% CI, 1.68-12.29		Grant from the Canadian Institutes of Health Research

Evidence Table 14. Long term harms in observational studies

Author, year Country	Study design	Study objective	Time period covered	Data source	Sample size	Population characteristics
Vestergaard, 2006 Denmark	Population-based case-control	To investigate if PPIs, histamine H_2 blockers, and other antacid drugs were associated with a decreased or increased fracture risk	2000	Registers managed by the National Board of Health, the Danish Medicines Agency, and the National Bureau of Statistics for administrative purposes	124,655 Cases 373,962 Controls	Mean age (years): 43.44 Male: 48.2% Cases vs Controls Previous fracture: 33.1% vs 15.0%

Evidence Table 14. Long term harms in observational studies

Author, year Country	Statistical methods	Effectiveness outcomes
Vestergaard, 2006 Denmark	Crude and adjusted ORs and 95% CI were calculated. Conditional logistic regression model was used	NR

Evidence Table 14. Long term harms in observational studies

Author, year Country	Safety Outcomes	Comments	Funder
Vestergaard, 2006 Denmark	Adjusted ORs for any fracture Last use of PPIs ≤ 1 year ago: 1.18 (95% CI, 1.12-1.43) Last use of PPIs > 1 year ago: 1.01(95% CI, 0.96-1.06) Last use of H_2 receptor blockers ≤ 1 year ago: 0.88 (95% CI, 0.82-0.95) Last use of H_2 receptor blockers > 1 year ago: 1.02 (95% CI, 0.97-1.07) Last use of other antacids ≤ 1 year ago: 1.33 (95% CI, 1.24-1.43) Last use of other antacids > 1 year ago: 1.02 (95% CI, 0.96-1.08) Last use of antihistamines ≤ 1 year ago: 1.04 (95% CI, 0.99-1.09) Last use of antihistamines > 1 year ago: 1.04 (95% CI, 1.00-1.07) Last use of NSAIDs ≤ 1 year ago: 1.70 (95% CI, 1.67-1.74) Last use of NSAIDS > 1 year ago: 1.12 (95% CI, 1.09-1.14)		The Danish Medical Research Council